DEVELOPMENT AND EVALUATION OF OSMOTICALLY CONTROLLED GLIPIZIDE EXTENDED RELEASE TABLET

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. Medical University,

CHENNAI - 600 032.

In partial fulfillment for the award of

Degree in

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

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Under the guidance of

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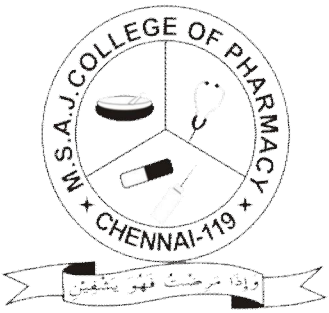

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This is to certify that this dissertation work entitled **"DEVELOPMENT AND EVALUATION OF OSMOTICALLY CONTROLLED GLIPIZIDE EXTENDED RELEASE TABLET"** submitted in partial fulfillment for the award of degree in Master of Pharmacy of The Tamilnadu Dr. M.G.R. Medical University, Chennai, is a bonafied work carried out by **Mr. KARTHIKEYAN. K, Reg. No: 261411204** under the guidance of **Mrs. Santha Sheela, M. Pharm., (Ph,D)., Associate Professor,** during the academic year 2015-2016.

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DECLARATION

I hereby declare that the dissertation work entitled **""DEVELOPMENT AND EVALUATION OF OSMOTICALLY CONTROLLED GLIPIZIDE EXTENDED RELEASE TABLET"** submitted the partial fulfillment for the award of degree in Master of Pharmacy under the Tamilnadu Dr. M.G.R. Medical University, Chennai was carried out by me under the guidance and supervision of **Mrs. N.B. Santha Sheela M. Pharm., (Ph.D)., Associate Professor**. I also declare that the matter embodied in it is a genuine work and has not been submitted for any other degree or diploma to this or any other university.

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Dedicated to

Brother (Late) Vijayakumar

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This book is written in dedication to the **God almighty** who has blessed me with the peace of mind, courage and strength and also with affectionate dedication to my loving family, parents, in laws, brother and friends, who throughout the years have given me lot of encouragement, valuable ideas and timely support whenever needed.

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K. **KARTHIKEYAN**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACRONYM	ABBREVIATION
%	Percentage
ºC	Degree Celcius
µg	Microgram
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
BD	Bulk Density
CA	Cellulose Acetate
CPOP	Controlled Porosity Osmotic Pump
CR	Controlled Release
Da	Dalton unit
DSC	Differential Scanning Calorimetry
EOP	Elementary Osmotic Pump
EU	European Union
f1	Difference Factor
f2	Similarity Factor
GI	Gastric irritation
HDPE	High Density Polyethylene
ICH	International Council for Harmonisation
LOD	Loss on Drying
L-OROS	Liquid – Oral Osmotic system
MCC	Cellulose, Microcrystalline
Mcg	Microgram
mg	Milligram

ACRONYM	ABBREVIATION
mL	Milliliters
mm	Millimeter
MW	Molecular Weight
OCDDS	Osmotic Controlled Drug Delivery System
OGD	Office of Generic Drugs
OROS – CT	Oral Osmotic system – Colon Targeting
PEO	Poly Ethylene Oxide
pH	Potential Hydrogen
PPOP	Push-Pull Osmotic Pump
PSI	Pounds Per Square Inch
PVP	Poly Vinyl Pyrolidone
RH	Relative Humidity
RPM	Rotation Per Minute
SOT	Sandwiched Osmotic Tablet/Pump
SPM	Semi-Permeable Membrane
TD	Tapped Density
US	United States
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
XRD	X-ray powder diffraction

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1 Oral Drug Delivery System:

Oral drug delivery is the most accepted and used route of administration when compared to all the other routes that have been known for the delivery of drugs[1]. Conventional oral drug delivery systems releases the drug immediately, in which its release of the drug cannot be controlled and cannot maintain effective concentration at the site of action or target for longer time[2]. These make the way forward for the development of other modified release drug delivery system. Most modified release delivery system classified into the following categories:

i. Delayed-release
ii. Extended-release
iii. Site-specific targeting
iv. Receptor targeting

All modified-release products improves the drug therapy over that achieved with their conventional counterparts. There are several potential advantages of modified release systems over conventional dosage forms such as

- ✓ Increase patient compliance
- ✓ Employ less total drug
  - Eliminate or minimize local side effects.
  - Eliminate or minimize systemic side effects.
  - Reduction or obtain less potentiation in drug activity with chronic use.
  - Minimize drug accumulation with chronic dosing.
- ✓ Improve efficiency in treatment
  - Cure or control condition promptly.
  - Improve control of condition (reduce fluctuation in drug level).
  - Improve bioavailability[3].

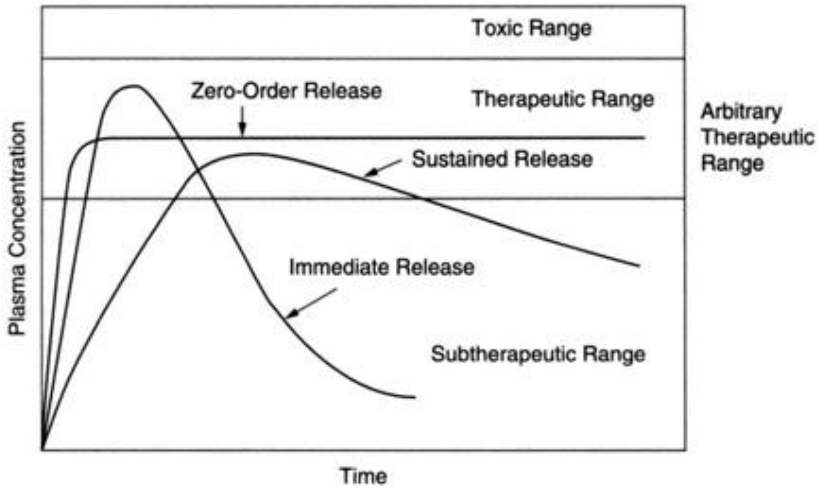


Figure-1: Drug level versus time profile [4]

1.2 Mathematical Models for Controlled-Release Kinetics[5]:

From a mathematical modeling point of view, according to physical mechanisms of the release of incorporated solute, the controlled-release systems can be classified. The majority of controlled-release systems depend on diffusion, dissolution or a combination of both to generate slow release of a drug. A variety of controlled release delivery systems are available based on this, they are:

1. Dissolution – controlled release
2. Osmotically – controlled release
3. Diffusion – controlled release
4. Chemically – controlled release
5. Miscellaneous – controlled release

1.3 Osmotic Controlled Delivery System:

Osmotic controlled delivery system works under the principle of osmosis. The main aim of the modified release is to control the delivery rate of the active ingredient, increasing the duration of therapeutic action and/or targeting its delivery to a specific tissue. These advances accomplished to the development of osmotic pumps, which are a form of a membrane-controlled release drug delivery system by using osmotic pressure as the source of energy. The fundamental aspect is that water permeates through a semi-permeable membrane that allows penetration of water without the active ingredient to dissolve its content, which is pushed off[6].

In this delivery system, water soluble active ingredient is combined with excipient and covered by a semi-permeable membrane in one chamber tablet. The membrane is not permeable to the active pharmaceutical ingredient; a small orifice is made in the coating by laser or mechanical during manufacturing. Inside the body, water enters into the tablet by osmosis, dissolving the API. The created pressure causes the API solution to go out through the hole and the device is therefore described as on osmotic pump dosage form. Finally, a steady state is reached where the rate of water entering through the membrane is the same as the rate of solution leaving the tablet. For a active moiety with limited solubility in water, a two-chamber (push-pull), osmotic pump tablet may be engaged.

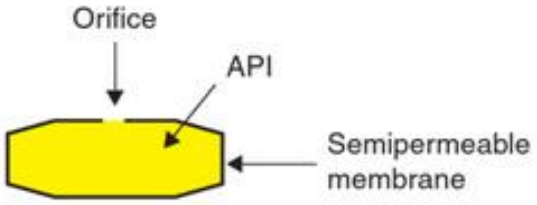


Figure-2: Schematic cross section of a one chamber osmotic pump[7]

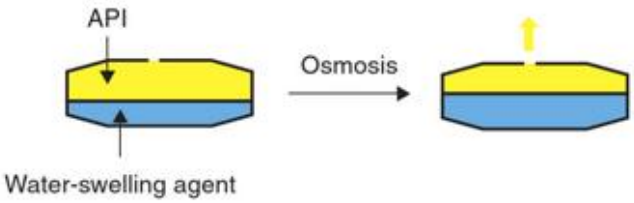


Figure-3: Mechanism of action of a two-chamber osmotic pump tablet[7]

In the formulated tablet, the API's release rate is dependent largely on the tonicity of body fluids. As this is constant, the API can be delivered at a defined rate. Because of the same reason, osmotic pump tablets are less exposed to interference from physiological conditions such as pH, presence of food.

The API's desired release rate can be controlled during formulation by modification of:

- ✓ The nature, surface area, thickness of the semi-permeable coating.
- ✓ The nature of medium supporting the API.
- ✓ The orifice size.
- ✓ The water-swelling osmotic agent's nature.

Using osmotic pump delivery, the API is released at a steady rate i.e. it tends to possess zero order kinetics (i.e. release rate is independent on drug) giving this approach an advantage over modified release dosage form. This principle can be used in the treatment of hypertension, arthritis and diabetic management[7]. There are over 357 patented osmotic drug delivery systems in US, EU, Japan etc.[8]

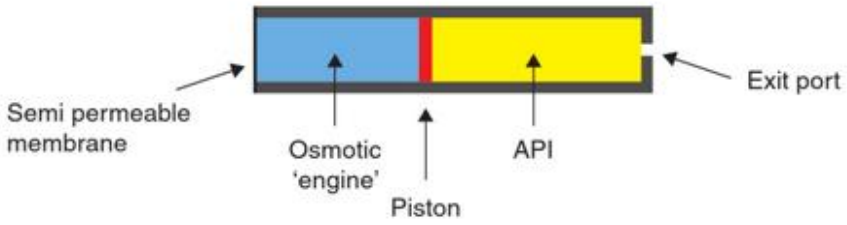


Figure-4: Schematic cross-section of a typical osmotic pump implant[7]

1.3.1 Osmosis:

Osmosis is the net movement of water from an area of high water concentration to an area of low water concentration through a semi-permeable membrane. A semi-permeable membrane is membrane which allows the movement of water but not other substances, through it[9]. Osmotic pressure is the pressure which, if applied to the more concentrated solution side would prevent inward flow of water across the semi-permeable membrane.

The first osmotic effect was reported by Abbe Nollet in 1748, later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. Pfeffer showed that the osmotic pressure of sugar solution is directly proportional to solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$$\Pi = Ø\ c\ RT$$

Where, Ø = osmotic pressure, Π = osmotic coefficient, c = molar concentration, R = gas constant, T = absolute temperature[10]

The osmotic water flow through a membrane is given by the equation[11]

$$dv\backslash dt = A\ Q\ \Delta\ \pi / L$$

Where

dv/dt = water flow across the membrane of area A in cm^2,

L = thickness,

Q = permeability and

$\Delta\ \pi$ = the osmotic pressure difference between the two solutions on either side of the membrane.

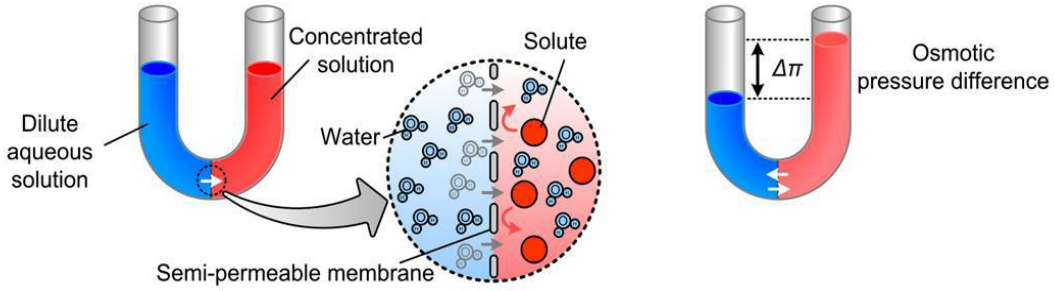


Figure-5: Principle of osmosis[12]

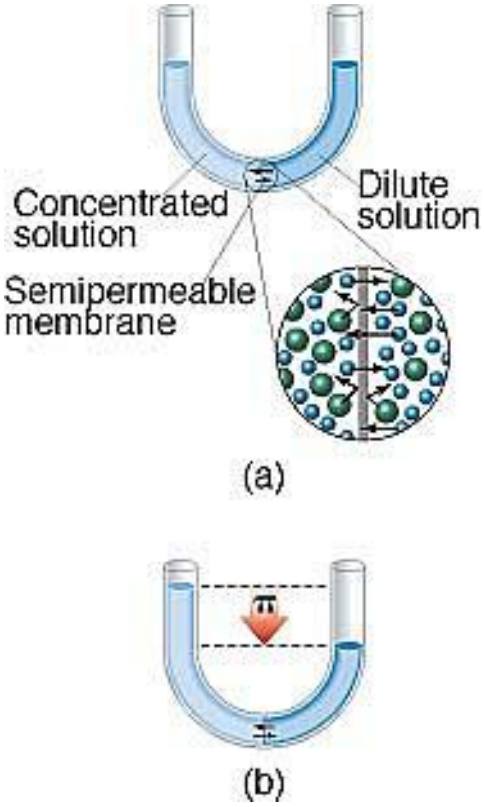


Figure-6: Osmosis
(a) Net movement of a solvent from the pure solvent with low solute concentration to a solution with high solute concentration;
(b) osmosis stops when the column of solution on the left becomes high enough to exert sufficient pressure at the membrane to counter the net movement of solvent. At this point the solution on the left has become more dilute, but there still exists a difference in concentrations between the two solutions[13]

1.3.2 Advantages and Disadvantages:

1.3.2.1 Advantages of Osmotic Controlled Drug Delivery[14]:

- ✓ Rate of drug release from osmotic systems is zero-order kinetics.
- ✓ Osmotic systems provide pulsed or delayed drug release.
- ✓ In comparison with diffusion controlled systems, osmotic systems attain a higher drug delivery rate.
- ✓ High degree of correlation with *in-vivo* delivery rate is observed.
- ✓ Delivery rate is unaffected by pH variations at the site, including the variation in the GI tract.
- ✓ Delivery rate is not affected by agitation from external sources including GI motility.
- ✓ Drug release rate from osmotic system is greatly predictable and programmable.
- ✓ Drug delivery takes place in the solution form, which is equipped for absorption, with osmotic pump acting as *in-situ* liquid dosage form.
- ✓ Delivery rate is mostly independent of delivery orifice size within limits.
- ✓ Drugs that exhibit broadly varying solubility pattern can be incorporated.

1.3.2.1 Disadvantages of Osmotic Controlled Drug Delivery:

- ✓ The costs of the osmotic devices are considerably higher than matrix tablets and multi-particulate capsules.
- ✓ When an osmotic tablet is subjected to magnetic resonance imaging, in case of non-uniform coating it may lead to different patterns of drug release.

1.3.3 Classification of Osmotic Drug Delivery System[14]:

A general classification consisting of oral and implantable systems can be considered as follows.

1.3.3.1 Implantable

1.3.3.2 Oral

1.3.3.3 Specific types

1.3.3.1 Implantable Osmotic Pumps**:**

1.3.3.1.1 Rose-Nelson Pump

1.3.3.1.2 Higuchi Leeper Pump

1.3.3.1.3 Higuchi Theuwes pump

1.3.3.2 Oral Osmotic Pumps**:**

The oral osmotic systems can be of various types which are as follows

1.3.3.2.1 Single chamber osmotic pump - Elementary Osmotic Pump

1.3.3.2.2 Multi chamber osmotic pump - Push pull osmotic pump

1.3.3.3 Specific types:

1.3.3.3.1 Controlled porosity osmotic pump

1.3.3.3.2 Osmotic bursting osmotic pump

1.3.3.3.3 Liquid Oral Osmotic System(L-OROS)

1.3.3.3.4 Delayed delivery osmotic device

1.3.3.3.5 Telescopic capsule

1.3.3.3.6 OROS – CT (Colon Targeting)

1.3.3.3.7 Sandwiched oral therapeutic system

1.3.3.3.8 Monolithic osmotic systems

1.3.3.3.9 Multi -Particulate Osmotic Pump

1.3.3.1 Implantable Osmotic Pumps:

1.3.3.1.1 Rose-Nelson Pump[15]:

Rose and Nelson, are the two scientists were the initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the drug delivery to the cattle and sheep gut.

The Rose-Nelson implantable pump shown in figure 7 is composed of 3 chambers

1. a drug chamber
2. salt chamber holding solid salt,
3. water chamber.

A semi-permeable membrane separates the salt from water chamber. The water movement from the water cavity towards salt cavity is influenced by difference in osmotic pressure across the membrane. Possibly, the volume of salt cavity increases due to water flow, which swells the latex diaphragm dividing the salt and drug chambers: finally, the drug is pumped out of the device.

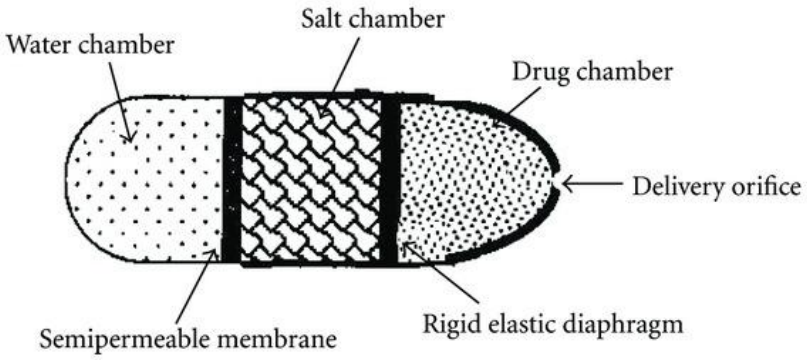


Figure-7: Rose-Nelson Pump[15]

The pumping kinetics from Rose Nelson pump is given by the following equation:

$$dMt / dt=(dV/dt).C, \ldots\ldots\ldots\ldots\ldots..(Eq.\ 1)$$

where *dMt/dt* is rate of drug release , *dV/dt* is volume of water flow into the salt cavity, and *C* represents the concentration of drug in the drug cavity.

$$dMt/dt = A\theta\Delta\pi C/l, \quad \text{…….(Eq. 2)}$$

where, A is the area of semi-permeable membrane, $\Delta\pi$ is the osmotic pressure gradient, θ is the permeability of semi-permeable membrane, and l is the thickness of semi-permeable membrane. These are applicable to the osmotically driven controlled drug delivery devices. The saturated solution creats a high osmotic pressure compared to that pressure required to pump the suspension of active agent. As a result, the water rate entering into the chamber of salt remains stable as long as sufficient solid salt is present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is created.

The major problem associated with Rose-Nelson pumps was that the osmotic action began whenever water came in get in touch with with the semi-permeable membrane. This wanted pumps to be kept empty and water to be loaded before use.

1.3.3.1.2 Higuchi-Leeper Osmotic Pump[15]:

Higuchi and Leeper have projected a number of variations of the Rose-Nelson pump and they have been described in US patents, which represent the simplifications of the Rose-Nelson pump made by the Alza Corporation. One of these pumps is illustrated in figure 8. The Higuchi-Leeper pump has no water cavity, and the device activation occurs after imbibitions of the water from the adjacent environment. This difference permits the device to be prepared loaded with drug and can be kept for long, prior to use. This pump contain a firm housing and a semi-permeable membrane supported on a perforated frame; a salt cavity containing a fluid solution with an excess of solid salt is usually available in this type of pump. Upon administration, nearby biological fluid enter into the device through porous and semi-permeable membrane and break downs the magnesium sulphate, creating osmotic pressure inside the device which pushes movable separator toward the drug cavity to remove drug outside the device. It is broadly used for veterinary use. This type of pump is fixed in body of an animal for delivery of antibiotics or growth hormones to animals

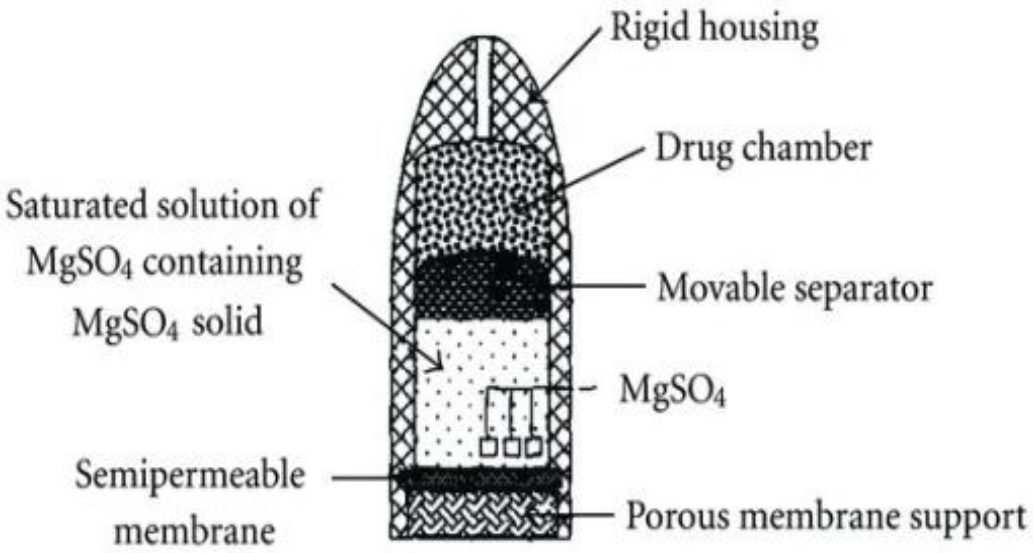


Figure-8: Higuchi Leeper osmotic pump[15]

Pulsatile delivery was achieved by using Higuchi Leeper pump; such modifications are described and illustrated in Figure 9. The Pulsatile release of drug is achieved by drilling the orifice in elastic material that stretches under the osmotic pressure. Pulse release of drug is obtained after attaining a certain critical pressure, which causes the orifice to open. The pressure then reduces to cause orifice closing and the cycle repeats to provide drug delivery in a pulsatile fashion. The orifice should be small enough to be substantially closed when the threshold level of osmotic pressure is not present.

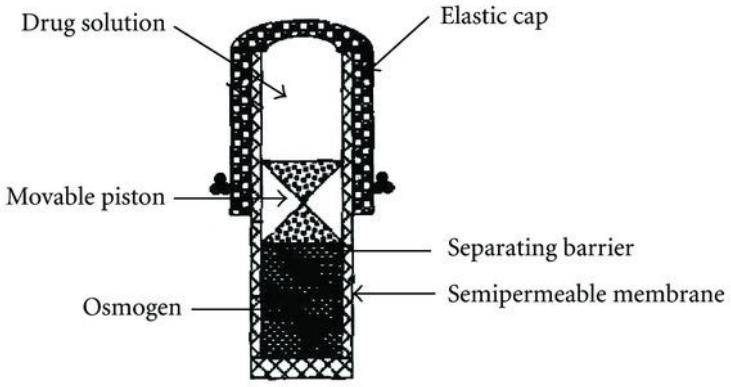


Figure-9: Pulsatile release osmotic pump[15]

1.3.3.1.3 Higuchi-Theeuwes Pump[15]:

Higuchi and Theeuwes in early 1970s developed another variant of the Rose-Nelson pump, even simpler than the Higuchi-Leeper pump as illustrated in Figure 10.

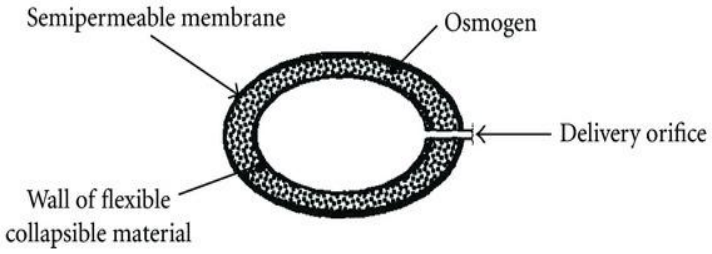


Figure-10: Higuchi-Theeuwes pump[15]

In this device, the rigid housing consisted of a semi-permeable membrane. This membrane is strong enough to withstand the pumping pressure developed inside the device due to imbibitions of water. Only prior to its application, the drug is loaded, which increases advantage for storage of the device for long time. The drug release from the device is managed by the salt used in the salt cavity and the permeability characteristics of the outer membrane.

Under trade name Alzet made by Alza Corporation in 1976, small osmotic pumps of this form are available. They are used frequently as implantable controlled release delivery systems in experimental studies requiring continuous administration of drugs. Such implantable Alzet pump is shown in Figure 11.

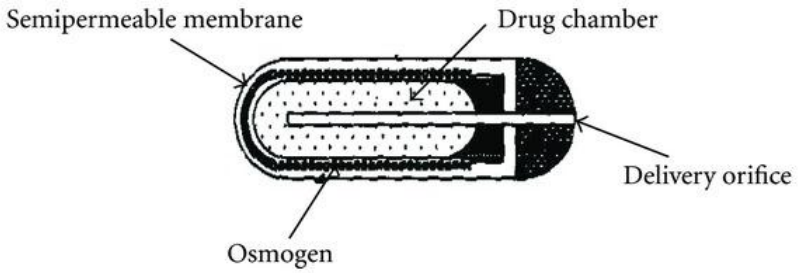


Figure-11: Alzet pump[15]

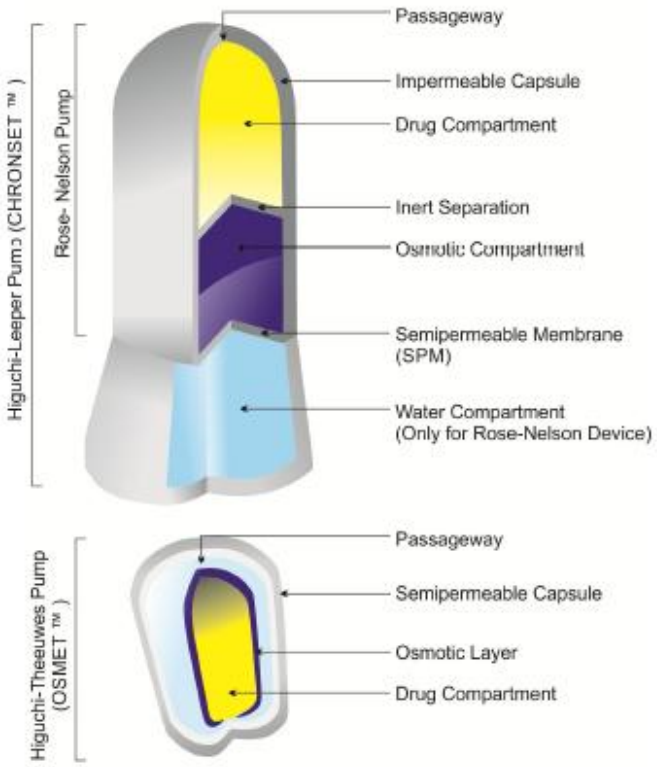


Figure-12: Higuchi Leeper osmotic pump and Higuchi- Theeuwes pump[16]

1.3.3.2 Oral Osmotic Pumps:

1.3.3.2.1 Elementary Osmotic Pump[15]:

Rose-Nelson pump was more simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. Elementary osmotic pump invented by Theeuwes in 1974 is shown in Figure 13 and contains an active ingredient having a fitting osmotic pressure. It is made as a tablet coated with semi-permeable membrane, usually with cellulose acetate. A small orifice is drilled through the membrane coating. While the coated tablet enters to an liquid area, the osmotic pressure of the drug inside the tablet draws water through the semi-permeable coating and a saturated aqueous solution of drug is made inside the device. The membrane is non-extensible and the increase in volume due to imbibitions of water raises the hydrostatic pressure inside the tablet, ultimately giving way to flow of solution which is saturated of active agent out of the device through a small hole.

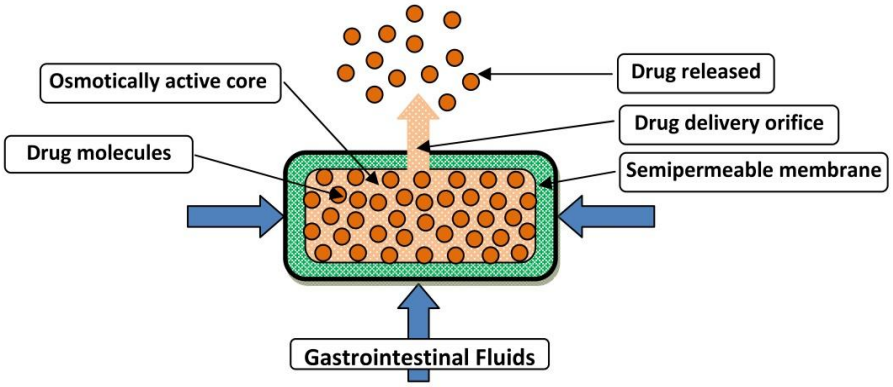


Figure-13: Elementary osmotic pump[17]

The pump initially releases the drug at a rate given by the following equation;

$$dMt/dt=(dV/dt).Cs\text{…….(Eq. 1)}$$

where, *dV/dt* represent the flow of water into the tablet and Cs is the solubility inside the tablet.

1.3.3.2.2 Push-Pull Osmotic Pump (PPOP) [15]:

Push-pull osmotic pump is an alteration of EOP (Figure 14). Push-pull osmotic pump is delivers both poorly water soluble and highly water soluble drugs at a constant rate. This system resembles a standard bi-layer coated tablet.

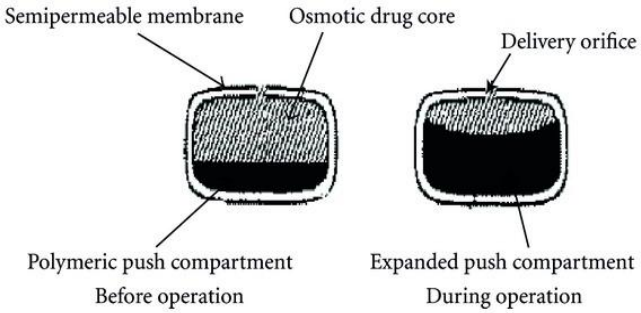


Figure-14: Push-pull based osmotic pump[15]

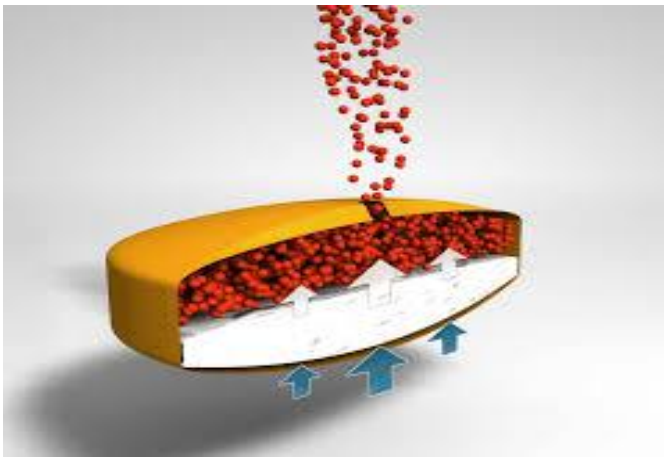


Figure-15: Cross section of push-pull osmotic pump[17]

One layer (the top one) contains drug in a formulation of polymer, osmogent, and other layer contains tablet excipients. This polymeric osmogent has the capacity to form a suspension of drug *in-situ*. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and attached together by tablet compression to form a single bi-layer core. The core tablet is coated with semi-permeable membrane. Once the coating is done, a small hole is placed by a laser or mechanical drill on the drug layer side of the tablet.

Mechanism:

When the system is entered in aqueous surrounding, water is attracted into the tablet by an osmotic agent in top and bottom layers. The osmotic attraction in the drug layer pulls water into the partition to form *in-situ* a suspension of drug. The osmogent in the non-drug layer simultaneously attracts water into that compartment, causing it to expand, and the drug suspension is sent out of the delivery orifice by the expansion of non-drug layer.

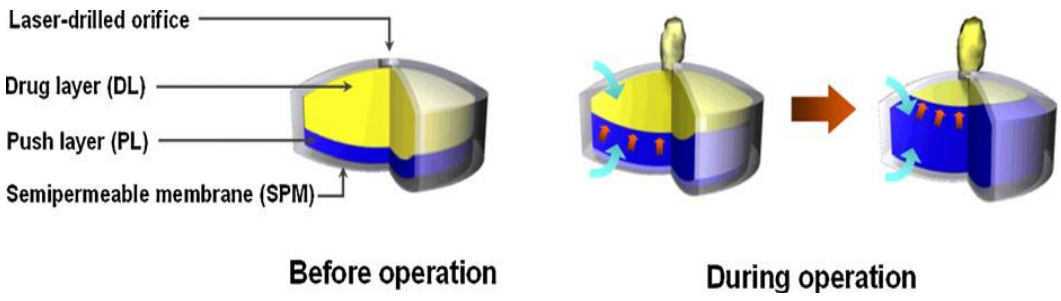


Figure-16: Mechanism of push-pull osmotic pump

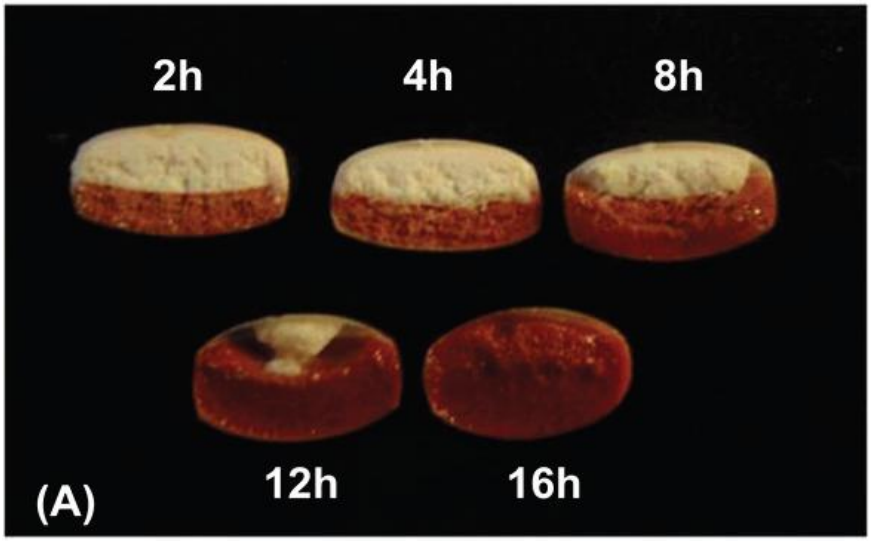


Figure-17: Push-pull pattern of PPOP tablets upon hydration in dissolution media over time[18]

1.3.3.3 Specific Types:

1.3.3.3.1 Controlled Porosity Osmotic Pump (CPOP)[15]:

Controlled porosity osmotic pump (CPOP) is shown in Figure 18. It is an osmotic tablet wherein the delivery holes are formed *in-situ* through escape of water soluble pore-forming agents included in semi-permeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from controlled porosity osmotic pump depends on various factors like thickness of coating, drug solubility in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane. CPOP system has many advantages. The stomach irritation problems are noticeably reduced, as drug is released from the whole of the device surface rather from a single hole. Further, no complicated procedure of laser-drilling unit is required because the holes are formed *in-situ*. Scheme describes the drug release phenomenon from a typical CPOP.

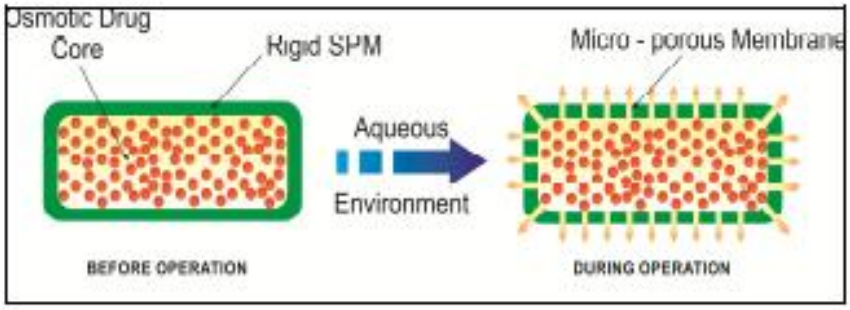


Figure-18 : Controlled porosity osmotic pump[19]

1.3.3.3.2 Bursting Osmotic Pump[19]:

There exists a close relationship between osmotic bursting osmotic pumps and elementary osmotic pumps. The major differences between the two types of osmotic pumps are the absence of a delivery orifice and the small size of the osmotic pump.

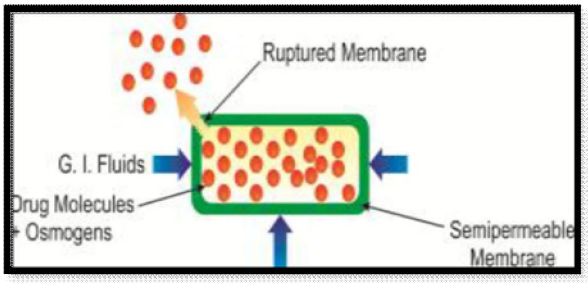


Figure-19: Bursting osmotic pump[19]

Mechanism of drug release:

When it is situated in an aqueous surrounding, water is absorbed and hydraulic pressure is developed inside the device until the wall bursts and the contents are released to the environment. In order to control the release, the thickness and the area of the semi-permeable membrane can be altered.

Advantages:

Changing the thickness as well as the area, the semi-permeable membrane can control the release of drug. This system is useful to provide pulsated release.

1.3.3.3.3 Liquid OROS[11]:

Liquid oral osmotic system are designed to deliver the drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types:

- L-OROS hard cap,
- L-OROS soft cap,
- Delayed liquid bolus delivery system

Each system includes a liquid drug layer, an osmotic engine or push layer and a semi-permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and the osmotic layer gets activated. The osmotic layer expands and results in the development of hydrostatic pressure inside the system, so the liquid formulation forced to get delivered through the delivery orifice. L OROS hardcap or softcap systems provide continuous drug delivery, the L OROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug. The delayed liquid bolus delivery system comprises of three layers: a placebo delay layer, a liquid drug layer and an osmotic engine, all surrounded by rate controlling semi-permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from 1 to 10 hours, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

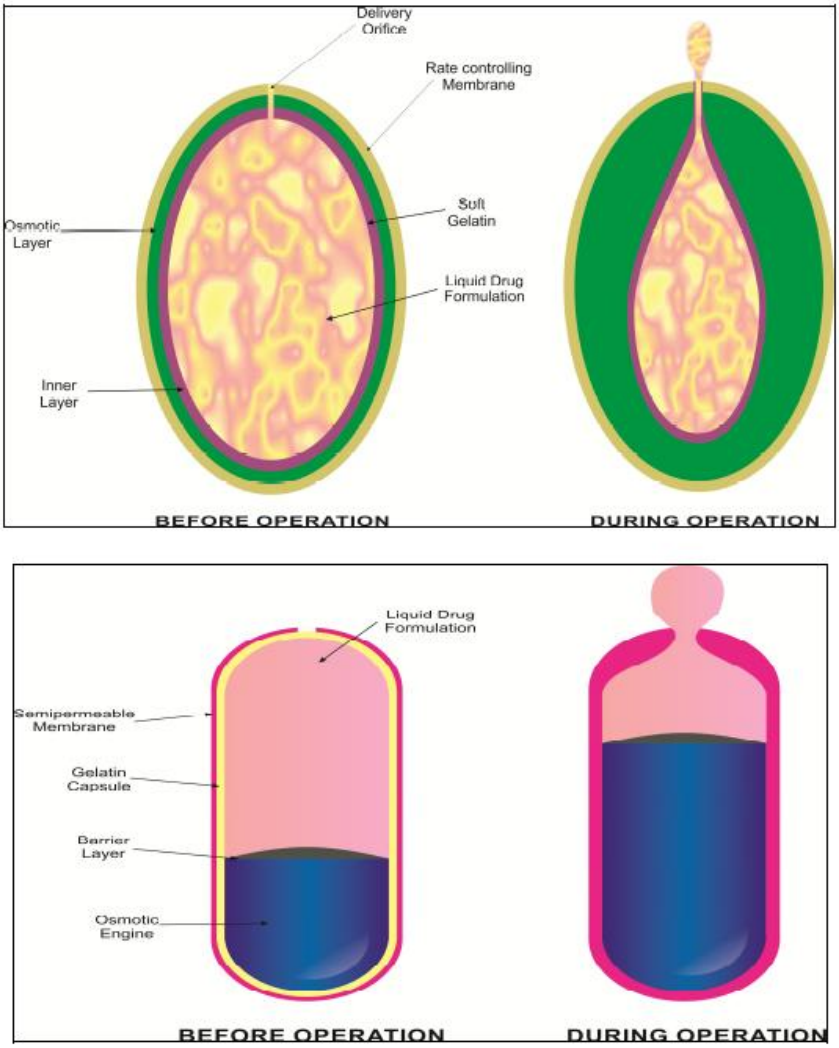


Figure-20: Liquid OROS[19]

1.3.3.3.4 Delayed Delivery Based on Multiple Coating[20]:

This osmotic device delivers fluid after a programmed and controllable time period. The osmotically driven pump can be made to a size suited for swallowing or implanting. This is used to administer a drug in a fluid form after an initial activation period during which essentially no drug is administered. The basic components are shaped semi-permeable membrane (SPM) that holds an osmotically effective solute and drug and a discharge port through which the drug is delivered. A micro-porous outer cover surrounds the semi-permeable membrane and protects it from an external aqueous environment. A water-swellable composition is kept between the end of the semi-

permeable membrane and the outer cover. As the pump is placed in an aqueous medium; water passes through the micro porous portion of the outer cover into the water swellable composition. The water-swellable composition absorbs water and it get expands, in piston-like fashion displaces the outer cover, thereby exposing the semi-permeable membrane to the aqueous medium and activates the osmotic pump. In initial activation period provided by water-swellable composition (time to absorb water, expand, and displace the outer cover) during which essentially no drug is delivered by the pump. By suitably adjusting the membrane composition and structure, a programmed activation period in the range of 3–18 h is achieved.

1.3.3.3.5 Telescopic Capsule[20, 21]:

It is the device for the immediate and extended delivery of an active agent during a prolonged period of time. The dispenser comprises first- and second-wall sections in a slideable telescoping arrangement (see Figure 21). The device consists of two chambers; the first contains the drug and an exit port, and the second contains an osmotic engine. The two sections are separated by wax-like material. The desired active agent is placed in one section by manual- or automated-fill mechanisms and the delivery device, is assembled. The bi-layer tablet with osmogent engine is kept inside the finished cap part of the capsule having osmotic layer with convex is pointed towards the closed end of the cap and the barrier layer exposed toward the opening of cap. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bi-layer tablet, and vessel fit together tightly.

The osmotic engine expands and exhibits pressure on the slideable connected first and second wall sections. This happens as fluid is entered through the dispensing device. In this delayed period, reservoir volume containing the active ingredient is kept constant; so, a minimal pressure gradient is available in between the environment of use and the reservoir interior. As a result, the net flow of outside fluid moved by the pressure to enter the reservoir is less, and as a result no agent is delivered for the period.

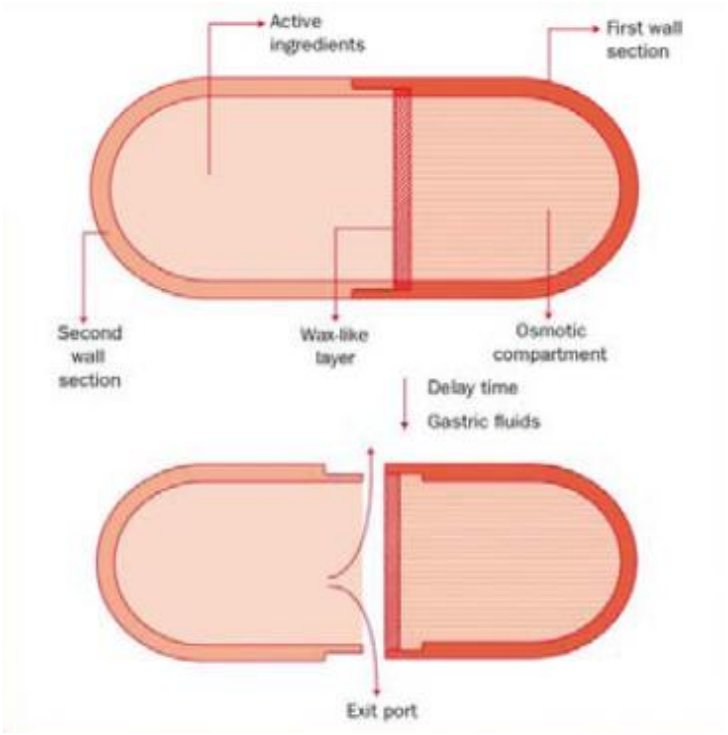


Figure-21: Principle of Telescopic capsule[15]

1.3.3.3.6 Colon Targeted Oral Osmotic System (OROS-CT)[14]:

It may consist of single unit osmotic device or as many as five to six osmotic unit filled in hard gelatin capsule. Enteric coating is provided for osmotic system.

Mechanism:

When GI fluids come in contact with gelatin capsule, shell dissolves. Entry of the fluid from stomach to the device is prevented by enteric coating and it dissolves after entering into intestine. Upon entry of the water, the push compartment swells and the formation of flowable gel happens which is pushed out through delivery orifice at a predetermined rate.

Application:

- Colon-targeting and
- Local or systemic therapy.

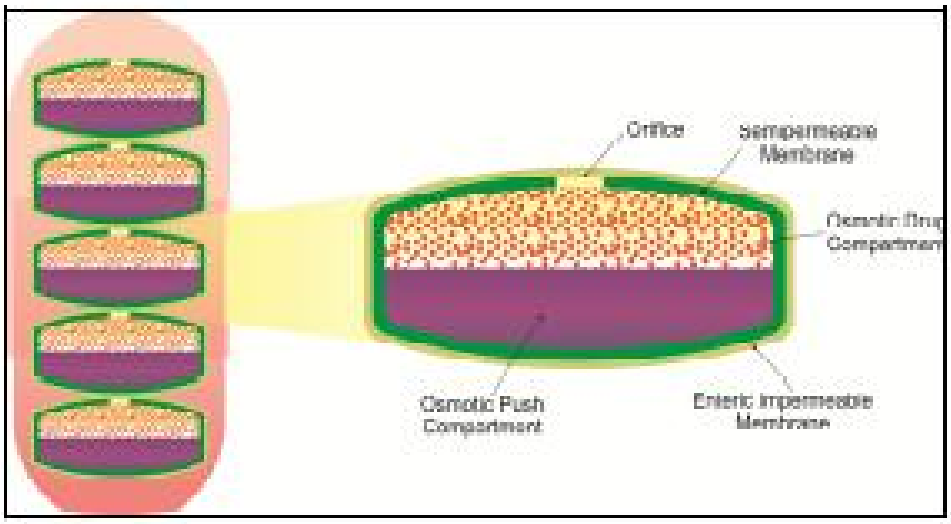


Figure-22: Colon targeted oral osmotic system[19]

1.3.3.3.7 Sandwiched Osmotic Tablet/Pump (SOT)[14]:

The SOT consists of coat and core. The coat consists of a semi-permeable membrane with delivery orifice on both the sides; semi-permeable membrane with two-side delivery orifice. The core tablet comprises of three layers: consists of two layers, which are attached, middle push layer with drug.

Mechanism:

When placed in the aqueous medium the push layer in middle swells and drug releases through delivery orifice.

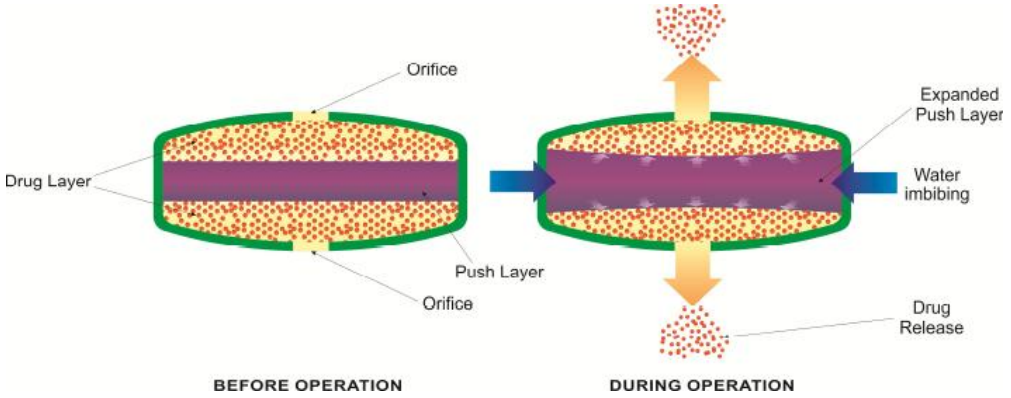


Figure-23: Sandwiched osmotic tablet[19]

1.3.3.3.8 Monolithic Osmotic Systems[11]:

This Monolithic osmotic system constitutes dispersion of water soluble compounds in polymer matrix. Water imbibitions by the active agent takes place when this system enters the aqueous region. This happens by rupturing the polymer matrix capsule surrounding the drug, thus liberating it out. This process starts occurring at the outer region of the polymeric matrix, but later it proceeds towards inside of the matrix. If 20 –30 volumes per liter of the active agents are incorporated, this system gets failed. significant contribution from the simple leaching of the substance take place.

1.3.3.3.9 Multi-Particulate Osmotic Pump[20]:

A tablet or capsule having large numbers of pellets bearing two or more pellets or particle population belongs to this type of osmotic pump. Every pellet has contains the therapeutic drug and a water-soluble osmotic agent as core. Each core encloses a water-permeable, water insoluble polymer film.

Hydrophobic agents that changes permeability (examples are fatty acid, wax, or a salt from a fatty acid) are incorporated into the polymer film. The speed of the water passes on the core and drug comes out of the core makes the film coating of each pellet to differ from the other pellets. The osmogent dissolves in water makes the pellet to swell and with that they control the speed of diffusion of drug. Drug released from each pellet population into the environment gives a chain of pulsatile administrations of the drug from a single dosage form.

Pellet populations may be varied because of coating thickness. In some cases, all of the active moiety in the dosage form may be found in a single population to provide a single pulse, which can be delayed by the release-controlling coating.

1.4 Formulation of Osmotic Controlled Drug Delivery System:

Following are the basic components of osmotic drug delivery system:

1.4.1 Drug[14]:

Drugs having less terminal half-life (between 1-6 hours) and potent drugs for extended treatment, much suits the requirement of osmotic controlled drug. Various drug candidates such as

- Paliperidone
- Glipizide
- Nifedipine are formulated as osmotic delivery.

1.4.2 Osmotic Agent[14, 22]:

Osmogents or the osmotic agents maintains the concentration gradient throughout the membrane. Pushing force is generated for taking up of water and helps in the hydrated formulation by maintaining drug uniformity. Ionic compounds consisting of either inorganic salts or hydrophilic polymers are the osmotic components. Sodium chloride, sulfates of sodium or potassium and lithium or potassium chloride can be the osmotic agents.

Osmotic agents can also be as sugars such as inorganic salts of carbohydrates glucose, sorbitol, or sucrose. The formulated polymers may be along with poly (cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly (alkali carboxy methyl cellulose), poly (ethylene oxide), and poly (alkylene oxide) are also included in the push layer of certain osmotic systems. Cyanamer (polyacrylamides), Carbopol (acidic carboxypolymer), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used.

Table-1: Osmotic agents and their examples

Osmogens	Example
Inorganic water-soluble osmogens	Sodium bicarbonate, Sodium sulphate, Magnesium sulphate, Sodium chloride, Potassium chloride
Organic polymer osmogens	Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Polyethylene oxide, Polyvinyl pyrrolidine, methyl cellulose
Carbohydrates	Arabinose, mannose, galactose, ribose, glucose, fructose, sucrose, maltose, lactose, xylose
Water-soluble amino acids	Alanine, glycine, leucine, methionine

1.4.3 Pore Forming Agents[14, 23]:

This pore forming agents are used in the development of controlled porosity or multiparticulate osmotic pumps and pumps developed for poorly water-soluble drug.

Microporous membranes are formed by these agents. Leaching occurs during the operation makes the formation of microporus *In-situ*. The gas formed within the coating polymer solution prior to the operation of the device creates pores in the wall.

The pore-formers should have the following characteristics: non-toxic, and on their removal, channels should be formed. The channels become a transport path for fluid.

- Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium sulphate, potassium phosphate etc.
- Alkaline earth metals such as calcium chloride, and calcium nitrate.
- Carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols.

1.4.4 Wicking Agent[22]:

A material with the ability to draw water into the porous network is said as wicking agent. It is of either swellable or non-swellable nature. They have the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via *Vander Waals* interactions between the surface of the wicking agent and the adsorbed molecule. Carrying water to surfaces inside the core of the tablet, and creating channels or a network of increased surface area is the function of the wicking agent.

Wicking agents, include titanium dioxide, sodium lauryl sulphate (SLS), colloidal silicon dioxide, kaolin, low molecular weight poly vinyl pyrolidone (PVP), alumina, niacinamide, m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene.

1.4.5 Flux Regulating Agents[14, 22]:

These are incorporated along with well-forming materials. Regulation of the fluid permeability of the flux through the wall is assisted by these agents. They can be preselected to enhance or reduce the liquid flux. They also segment the flexibility and porosity of the lamina.

- Flux enhancing agents: hydrophilic substances such as polyethylene glycol (300-6000 Da), polyhydric alcohol, poly alkylene glycol.
- Flux reducing agents: hydrophobic substances such as pthalates substituted with an alkyl or alkoxy, example: diethyl phthalate, dimethoxy ethyl phthalate.

1.4.6 Semi-Permeable Membrane[11, 14, 23]:

An important part of the osmotic drug delivery system is the semi-permeable membrane. The important feature of semi-permeable membrane utilized for an osmotic pump is that it permits only the passage of water into the unit and thereby effectively isolate the dissolution process from the gut environment. Therefore, the polymeric membrane selection is more important in the osmotic drug delivery formulation.

1.4.6.1 Ideal Property of Semi-Permeable Membrane:

- Membrane should meet some performance criteria:
- The material must possess sufficient wet strength (-105) and wet modulus to retain its dimensional integrity during the operational lifetime of the device.
- The membrane exhibits sufficient water permeability, so that it retain water flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
- The reflection co-efficient and leakiness of the osmotic agent should approach the limiting value of same. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
- The membrane should also be biocompatible.
- Rigid and non-swelling.
- It should be sufficiently thick to withstand the pressure within the device.

Polymers that are permeable to water can be used as a coating material in osmotic devices example: Cellulose acetate, agar acetate, betaglucan acetate, ethyl cellulose, polyether copolymer, olyacetals, polyglcolic acid, polyactic acid, sulfonated polystyrenes, polyurethanes.

1.4.7 Coating Solvent[2,23]:

Solvents suitable for making polymeric solutions, that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core wall and other excipients in osmotic drug delivery. And few examples of coating solvent are methylene chloride, methanol, isopropyl alcohol, dichloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol(80:20), methylene chloride- methanol (79:21), acetone-ethanol (80:20), methylene chloride-methanol-water (75:22:3).

1.4.8 Plasticizers[22]:

Plasticizers lower the temperature of the second order phase transition of the wall or the elastic modules of the wall. It also increase the workability, flexibility and permeability of the fluids.

Plasticizer from 0.001 to 50 parts or a mixture of plasticizers are incorporated in to 100 parts of wall forming materials.

Suitable polymers should have a high degree of solvent power for the materials, compatible with the materials over both the processing and the temperature range, exhibit permanence as seen by their strong tendency to remain in the plasticized wall, impart flexibility to the materials and should be non-toxic.

Examples: dialkyl phthalates and other phthalates, trioctyl phosphates and other phosphates, alkyl adipates, triethyl citrate and other citrates, acetates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides and halogenated phenyls.

1.5 General Mechanism For Drug Release From Osmotic Pumps [11]:

The basic equation which applies to osmotic systems is

dM/dt = dV/dt . c …….(Eq. 1)

Where,

dM/dt= mass release,

dV/dt= volumetric pumping rate,

c = concentration of drug.

But, dV/dt = (A/ h) Lp (σ Δπ -Δp) ……. (Eq. 2)

Where,

A = membrane area,

h = thickness of membrane,

Lp= mechanical permeability,

σ = reflection coefficient,

Δπ = osmotic pressure difference,

Δp = hydrostatic pressure difference.

As the size of orifice delivery increases, Δp decrease, so Δπ >> Δp and equation becomes

dV/dt = A/ h Lp (σ Δπ) …….(Eq. 3)

When the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, p can be substituted for Dp.

dV/dt = A/h Lp σπ = A/hk π …….(Eq. 4)

(k = Lpσ = membrane permeability)

Now, equation (1) can be given as

dM/dt = (A/h) k π c = (A / h) k π S …….(Eq.5)

S = solubility of drug, c taken as S

1.6 Factors That Influence The Release Rate In The Osmotic Controlled Drug Delivery Systems:

1.6.1 Drug Solubility[19]:

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core. Assuming that a tablet core of pure drug, with zero-order kinetics, the fraction of core released is given by equation.

$$F(z) = 1 - S/\rho \quad \text{.....(Eq. 1)}$$

Where,

F(z) is the fraction released by zero-order kinetics,

S is the drug's solubility (g/cm^3),

ρ is the density (g/cm^3) of the core tablet.

Drugs with a density of 1 and the solubility of ≤ 0.05 g/cm^3 would be released with greater than or equal to 95% zero-order kinetics, according to Eq. (1).

At the same time, high release rates were demonstrated with highly water-soluble drugs that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump.Water solubility of osmotic drugs ranges 50–300 mg/ml.

Some of the approaches that have been used to modulate drug solubility within the core include:

(1) co-compression of the drug with excipients, which modulate the drug's solubility within the core.

(2) Use of effervescent mixtures to increase the release of poorly soluble drug from the orifice.

(3) Use of cyclodextrin derivatives to increase the solubility of poorly water soluble drug.

(4) Use of alternative salt form that has optimum water solubility.

(5) Use of encapsulated excipients.

(6) Use of lyotropic crystals.

1.6.2 Osmotic Pressure[19]:

The next release-controlling factor that must be optimized is the osmotic pressure gradient between the compartment which is inside and the external environment.

The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet. Polymeric osmagents are mainly used in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state.

Table-2: Osmotic pressure of different compound and its mixture.

Compound or Mixture	Osmotic Pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose- Fructose	430
Mannitol-Fructose	415
Sodium chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribase $12H_2O$	36
Sodium phosphate dibasic $7H_2O$	31
Sodium phosphate dibasic $12H_2O$	29
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic H_2O	28

1.6.3 Size of Delivery Orifice[15]:

To get zero-order delivery profile, area of the orifice must be sufficiently large to minimize osmotic pressure build up in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained optimum between the minimum and maximum values; orifice size is generally between 600 microns to 1 mm.

Methods to create a delivery orifice in the osmotic systems are:

1. Mechanical drilling: Done by manually drilling the orifice by special bench top equipment or by using needle to get the required diameter of the delivery orifice.
2. Laser drilling: This technology is well established for producing sub-millimetre size hole in tablets. Normally CO_2 laser beam is used for drilling purpose, which offers excellent reliability.
3. Indentation: In this type core tablets are made by using modified punches having needle on upper punch. The hole made by the indentation is not covered during coating process which acts as a path for drug release in osmotic system.
4. Use of pore forming substances in the semi-permeable membrane coating: e.g. controlled porosity osmotic pump.

1.6.4 Semi-Permeable Membrane[19]:

Some of the membrane variables that are important in the design of oral osmotic system are:

- Type and nature of polymer:

  Any polymer permeable to water but impermeable to solute can be selected.

- Membrane thickness:

  Thickness of the membrane has a marked effect on the drug release from osmotic system, which is inversely proportional to each other.

- Type and amount of plasticizer:

  In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscoelastic behavior of

polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

1.7 Advances in Osmotic Drug Delivery[24]:

Duros Technology:

The DUROS pump conceptually resembles a miniature syringe in which drug is pushed out in highly controlled, minute dosages. Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by salt (osmotic agent) residing in the engine compartment. The water drawn into the engine compartment expands the osmotic agent and slowly and continuously displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice.

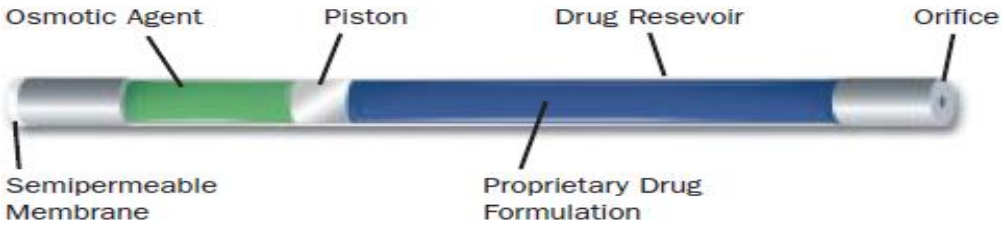


Figure-24: Duros technology[24]

DURECT is holding an exclusive license from ALZA Corporation to develop and commercialize products in selected fields based on the DUROS® implant technology.

1.8 Marketed Products[19]:

Table -3: Marketed products of osmotic drug delivery system

Trade Name	Active ingredient	Design system	Dose
Alpress LP	Prazosin	Push -Pull	2.5 - 5 mg
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Cardura XL	Doxazosin	Push -Pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg
Ditropan XL	Oxybutinin chloride	Push -Pull	5, 10 mg
Dynacirc CR	Isradipine	Push -Pull	5, 10 mg
Invega	Paliperidone	Push -Pull	3, 6, 9 mg
Efidac 24	Chlorpheniramie maleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push - Pull	5, 10 mg
Minipress XL	Prazocine	Elementary pump	2.5, 5 mg
Procardia XL	Nifedipine	Push - Pull	30, 60, 90 mg
Sudafed 24	Pseudoephedrine	Elementary pump	240 mg
Volmax	Sabutamol	Elementary pump	4, 8 mg
Tegretol XR	Carbamazepine	oros	100, 200, 400mg
Viadur	Leuprolide acetate	Implantable osmotic systems	-----
Chronogesic	Sufentanil	Implantable osmotic systems	-----
Concreta	Methylphenidate	Implantable osmotic systems	18, 27, 36, and 54 mg

2. LITERATURE REVIEW

Suryavanshi V *et al*., [25] (2016) evaluated push pull osmotic pump-based drug delivery system for controlled release of Isoxsuprine hydrochloride for peripheral and cerebral vasodilation. Effects of different variables like amount of osmogen, orifice size, coating thickness and dissolution media were studied on release profile. Studies concluded that the osmotic pump tablets could provide more prolonged and controlled release that may result in an improved therapeutic efficacy and patient compliance.

Zala Parth Harishkumar *et al*., [26] (2015) formulated and evaluated the controlled porosity osmotic pump drug delivery for Pregabalin. Controlled porosity of the membrane is accomplished by the use of channeling agent. Sodium chloride was used as osmogent. Cellulose acetate was used as the semi permeable membrane. The effect of ratio of drug to osmogent, membrane weight gain, concentration of pore former, and effect of pH and agitation intensity on drug release was also studied. It was found that drug release rate increased with the amount of osmogent because of increased water uptake, and hence increased driving force for drug release. Drug release was inversely proportional to membrane weight gain: however, directly related to the concentration of pore former in the membrane.

Sailaja Reddy Karri *et al*., [27] (2014) prepared and experimented push-pull osmotic tablets for Nateglinide for the treatment of hyperglycemia (type 2 diabetes) which has a half-life of 1.5 h. Evaluation studies were performed for weight variation, hardness test and found to be within the limit. Dissolution was also performed and the release profile of formulation F is 91.75%, F1 was 60.89%, F2 was 76.985% and F3 was 83.16% for 12 h. It has been concluded that push-pull osmotic tablet was able to deliver the drug in a controlled pattern for a prolonged period. This type of formulation can be used in conditions like hyperglycemia where the patient compliance can be improved by reducing the dosing frequency and the plasma drug levels can be maintained, the total drug load is also reduced so that the dose related side effects are also reduced.

Millin R Gohel *et al*., [28] (2014) formulated and optimized a push-pull osmotic controlled drug delivery system for highly water soluble drug like ropinirole hydrochloride which can release drug in controlled manner for extended period. Push-pull osmotic system showed the desired

once-a-day release kinetic. This method may improve patient benefits by providing enhanced efficacy and reduced side effects and may also reduce the number of daily doses compared to conventional therapies. All the evaluation parameters of tablet like hardness, friability, drug content, drug release study, etc. were satisfactory. The stability study revealed that the optimized batch which was subjected to accelerated stability study shows no significant changes and confirms the stability of formulations.

Patel GC *et al.*, [29] (2014) developed controlled release osmotic pump tablets (COPT) of glipizide (GZ) solid dispersion (SD). The SDs having different ratio of drug to Poloxamer (PXM) 188 were prepared by hot melt method and optimized by solubility study, drug content estimation and *in-vitro* dissolution study. Effect of two independent variables, amount of osmogen (potassium chloride) and hydrophilic polymer (polyethylene oxide WSR 303), were investigated using 3 factorial design. Core and coated tablets were evaluated for pharmacotechnical parameters. *In-vitro* drug release profiles of COPT tablets were compared with marketed push-pull osmotic pump tablet Prepared core and coated tablets showed acceptable pharmacotechnical parameters. Drug release was directly proportional to initial level of hydrophilic polymer, but inversely related to the osmogen, confirming osmotic mechanism. Zero order drug release pattern was achieved which was comparable to marketed product. Novel oral controlled release of glipizide was successfully achieved by incorporating glipizide solid dispersion into osmotic system.

Preethi N *et al.*, [30] (2013) developed novel type of elementary osmotic pump [EOP] tablet for efficient delivery of poorly water-soluble drug, glipizide. The effect of wetting agent, swelling agent, osmotic agent and hydrophobic plasticizer on the release rate were investigated. Compared with the marketed Glipizide extended release tablet; GF2 gave the best release rate for 24 hours. The bioavailability studies for glipizide SEOP and Glipizide extended release tablet was carried out in albino rabbits and there was a good *in-vivo* and *in-vitro* correlation for GF2 as shown by the higher C_{max} and AUC values. Thus a novel SEOP was successfully formulated for glipizide to achieve zero order drug release over a period of 24 hours.

Garvendra S Rathore *et al*., [31] (2012) developed and evaluated the controlled porosity osmotic pump (CPOP) based drug delivery system of sparingly water soluble drug atenolol (ATL). Formulation variables, such as, the levels of solubility enhancer (0-15% w/w of drug), ratio of the drug to the osmogent, coat thickness of the semi-permeable membrane (SPM) and level of pore former (0-20% w/w of polymer) were found to effect the drug release from the developed formulations. Cellulose acetate (CA 398-10) was used as the semi-permeable membrane containing polyethylene glycol 400 as the plasticizer. ATL release was directly proportional to the level of the solubility enhancer, osmotic pressure generated by osmotic agent and level of pore former; however, was inversely proportional to the coat thickness of SPM. Drug release from developed formulations was independent of the pH and agitation intensities of release media. Burst strength of the exhausted shells decreased with increase in the level of pore former. The optimized formulations were subjected to stability studies and they were found to be stable after 3 months study.

Patel P *et al*.,[32] (2012) studied the influence of dose and solubility of four model drugs on push-pull osmotic pumps and found that standard push-pull osmotic pump system may be suitable for a wide range of drugs of varying solubility and doses (below 25% w/w of pull layer formulation). This investigation demonstrated the robustness and flexibility of the push-pull osmotic pump system for various model drugs.

Shahla Jamrzad *et al*., [33] (2012) studied the influence of level and location of Nacl on performance of push pull osmotic pump tablet of a practically water insoluble model drug. Drug release profiles were not significantly affected by osmogen concentration in the push layer in the range of 10-35% w/w. Presence of osmogen in pull layer resulted in shorter lag time and greater drug release rate. The findings of this study illustrated robustness of osmotic technology for zero order drug release and approaches to modulate drug release using the osmogen concentration and location.

Sharma AR *et al*., [34] (2012), developed push pull osmotic drug delivery for a highly insoluble drug, they studied the effect of orifice diameter, polymer concentration in drug layer coating composition, were tested, and promising results were found. The drug release was independent

of pH but dependent on the osmotic pressure of the dissolution medium the release kinetics followed the zero order models.

Avinash Singh *et al*., [35](2011) developed extended release formulations of Anti diabetic drug using osmotic technology and studied the influence of tablet core variables, including amount of sodium chloride in drug layer, carbopol 934p amount in push layer and drug layer, effect of ph , orifice size, agitation intensity, weight gain by coating, and *in-vitro* drug release. They observed that drug release rate increased significantly as the amount of sodium chloride and carbopol increase. Drug release was inversely proportional to the coating thickness, but directly proportional to the orifice size. The manufacturing procedure was standardized and found to be reproducible.

Afifa Bathool *et al*., [36] (2011) developed Microporous osmotic tablet of diltiazem hydrochloride for colon targeting. The tablets were prepared by wet granulation method and coated with microporous semipermeable membrane and enteric polymer using conventional pan coating process. The effect of formulation variables was studied by changing the amounts of sodium alginate and NaCMC in the tablet core, osmogen, and that of pore-forming agent (SLS) used in the semipermeable coating. Drug release was increased as the concentration of osmogen and pore-former was increased. Fourier transform infrared spectroscopy and Differential scanning calorimetry results showed that there was no interaction between drug and polymers. Scanning electron microscopic studies showed the formation of pores after predetermined time of coming in contact with dissolution medium. The formation of pores was dependent on the amount of pore former used in the semipermeable membrane. *In-vitro* results showed acid-resistant, timed release at an almost zero order up to 24 hours. The developed osmotic tablets could be effectively used for prolonged delivery of Diltiazem HCl.

Piyush Patel *et al*., [37] (2011) studied the effect of granulation parameters like inclusion and exclusion of milling of dried granules, use of chopper during granulation on the performance of push pull osmotic tablet of a practically water insoluble drug. The results of the study showed that although differences were observed in the physical properties of the resulting granules drug release from the push pull osmotic system was not significantly affected.

Shahla Jamzad *et al*., [38] (2006) developed a new monolithic matrix system to completely deliver Anti diabetic drug in a zero order manner. Two approaches were examined using drug in formulation that contain swellable hydroxyl propyl methyl cellulose or erodible polyethylene oxide. The matrices were prepared by dry blending selected ratios of polymers and ingredients using direct compression technique. The interrelationship between matrix hydration, erosion and textural properties were determined and analysed under the dissolution test conditions. Hydroxyl propyl methyl cellulose matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to polyethylene oxide matrices. Results indicated that in the case of low dose/low soluble drug, total drug release in a zero order manner depends on the synchronization of erosion and swelling fronts during the entire dissolution study.

Ouyang *et al*.,[39] (2005) developed a simple elementary osmotic pump system that could deliver combinational two Anti diabetic drugs for extended periods of time in order to reduce the problems associated with multidrug therapy of type 2 non-insulin-dependent diabetes mellitus. It showed good sustained effect in comparison with the conventional product. The prototype design of the system could be applied to other combinations of drugs used for cardiovascular diseases, diabetes, etc.

Verma RK *et al*., [40] (2004) developed and evaluated extended release formulation of glipizide based on osmotic technology. The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Burst strength of the exhausted shells increased with the weight gain of the membrane. On the other hand, burst strength decreased with an increase in the level of pore former in the membrane. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane. Manufacturing procedure was found to be reproducible and formulations were stable after 3 months of accelerated stability studies.

Thombre *et al*.,[41] (2004) developed a swellable-core technology (SCT) formulations that used osmotic pressure and polymer swelling to deliver drugs to the GI tract in a reliable and reproducible manner. The swellable-core technology formulations consisted of a core tablet containing the drug and a water-swellable component, and one or more delivery ports. The *in-vitro* and *in-vivo* performance of two model drugs, tenidap and sildenafil, formulated in four different swellable-core technology core configurations: homogeneous-core (single layer), tablet-in-tablet, bilayer, and trilayer core were evaluated.

Gan Y *et al*., [42] (2003) developed Anti diabetic drug – cyclodextrin inclusion complex osmotic pump tablets. Polyethylene glycol 4000 and cellulose acetate were selected as the coating materials, and acetone–water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push–pull osmotic tablet. The results indicated that Anti diabetic drug–cyclodextrin inclusion complex osmotic pump tablets had excellent zero-order release characteristics *in-vitro*.

Zhang Y *et al*.,[43] (2003) prepared a novel pulsed-release system based on bilayer coated tablets containing an osmotically active agent. Hydroxypropylmethylcellulose and the mixture of Eudragit RS and RL were applied as the swelling layer and semi permeable outer coat, respectively. To examine the mechanism of drug release from this pulsed-release system, drug release behaviors were investigated under conditions of various osmotic pressures. Both lag time and release rate were dependent on the coating level and the osmotic pressure of the dissolution medium.

3. AIM AND OBJECTIVE

3.1 Aim

- To develop and evaluate a push-pull based osmotic delivery system for anti-diabetic drug (Glipizide).

3.1.1 Objective

- To develop push-pull based osmotic delivery system of anti-diabetic drug, belonging to BCS class II and optimize a generic formulation to the innovator.

4. Work Plan

4.1 Pre-formulation studies

- 4.1.1 Organoleptic properties
- 4.1.2 Solubility
- 4.1.3 Melting point
- 4.1.4 X-ray diffraction
- 4.1.5 Hygroscopic studies
- 4.1.6 Sieve analysis
- 4.1.7 Moisture content of API
- 4.1.8 Density:
  - 4.1.8.1 Bulk Density
  - 4.1.8.2 Tapped density
  - 4.1.8.3 Carr's Index
  - 4.1.8.4 Hausner's Ratio
  - 4.1.8.5 Angle of repose
- 4.1.9 Drug-Excipient compatibility study

4.2 Characterization of Innovator Product

- 4.2.1 Physical Properties
  - 4.2.1.1 Description
  - 4.2.1.2 Average weight
  - 4.2.1.3 Thickness
  - 4.2.1.4 Hardness
  - 4.2.1.5 Dissolution profile

4.3 Analytical parameters

- 4.3.1 Determination of λ_{max}
- 4.3.2 Plotting of calibration curve

4.4 Formulation of OCDDS

- 4.4.1 Optimization of core tablet formula
  - 4.4.1.1 Optimization of PEO in push and pull layers
  - 4.4.1.2 Optimization of osmogent in push layer
- 4.4.2 Optimization of the semi permeable membrane (coating of the core tablet)

4.5 Evaluation of Osmotic tablets

4.5.1 Assay

4.5.2 Weight variation

4.5.3 Hardness

4.5.4 Friability

4.5.5 Thickness

4.5.6 Coating uniformity

4.5.7 *In-vitro* drug release and comparison with innovator

4.6 Evaluation of Osmotic tablets

4.6.1 Comparison of dissolution testing between innovator and prepared Anti-diabetic tablets.

4.7 Stability studies

5. SCOPE OF THE WORK

Osmotically controlled drug delivery systems (OCDDS), is a novel drug delivery system that utilizes the principles of osmotic pressure for the controlled delivery of drug. Osmotic devices are most promising strategy based system for controlled drug delivery and are designed to follow true zero-order kinetics and thus high degree of *in-vitro / in-vivo* correlation can be achieved.

Drug release from these systems is also independent of pH, food and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.

An anti-diabetic drug, Glipizide falling under BCS class-II drug was selected for the development of OCDDS due to its short biological half-life (2-4 hrs), high potency, and need for prolonged treatment.

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class to improve glycemic control as an adjunct to diet in adults with type 2 diabetes mellitus, a BCS Class-II drug.

The conventional formulation of this drug possesses problems like frequent dosing and large fluctuation in drug plasma concentration. Moreover, it may cause adverse gastrointestinal reactions. This indicates need to develop controlled release formulations for these drugs. Thus, OCDDS was selected for development of CR formulation of these drugs.

In the present study double chambered Push Pull Osmotic Pump (PPOP) is chosen, because this technique is proved as simple, inexpensive and having industrial feasibility. This system relies on semi permeable membrane to function. This system is characterized by the different parameters like weight variation, hardness, friability, drug content, and *In vitro* drug release studies etc.

Thus, the scope of present study was to formulate, optimize and characterize osmotically controlled drug release systems for selected drug using Push Pull Osmotic Pump (PPOP) technique. Optimized batch was subjected stability study as per ICH guidelines. The

study also focused comparison of developed formulation made by innovator and identifying optimized generic formulation to innovator.

6. DRUG AND EXCIPIENT PROFILE

6.1 Drug Profile[44]:

Drug Name: Glipizide

Chemical Structure:

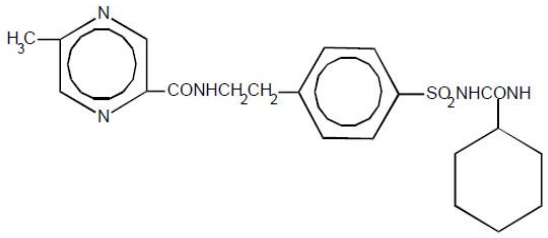


Figure-25: Structure of Glipizide

Chemical Name: 1-cyclohexyl-3-[[p-[2-(5 ethylpyrazinecarboxamido) ethyl] phenyl] sulfonyl] urea

Chemical Formula: $C_{21}H_{27}N_5O_4S$

Molecular Weight: 445.55

Category: Anti-diabetic

Description: Whitish, odorless powder

Solubility: It is insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethyl formamide.

Strengths: 2.5mg, 5mg and 10mg.

BCS Class: Class II (Low Soluble – High Permeable)

Pharmacokinetics: Gastrointestinal absorption of Glipizide in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1–3 hours after a single oral dose. The elimination half-life ranges from 2–4 hours in normal subjects, whether given

intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Thus, Glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding found to be 98–99% one hour after either route of administration. The metabolism is extensive and occurs mainly in the liver. Less than 10% unchanged glipizide is found in the urine.

Mechanism of Action: The primary mode of action of Glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans, Glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glipizde lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extra pancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Indication and Dosage: Management of type 2 diabetes (Non Insulin Dependent Diabetes Mellitus) where diet control alone is not effective in controlling the hyperglycemia. Dosage should be given to patients individually, on basis of periodic tests of glycosuria and blood sugar. The maximum daily dose should not exceed 30 mg as maintenance dose.

Contraindication: Glipizide is contraindicated in Insulin dependent diabetes mellitus, diabetic-keto-acidosis, diabetic coma, pregnancy, in subjects with severely impaired kidney or liver function, adrenal insufficiency and cases of confirmed individual

hypersensitivity to the drug, latent diabetes or pre-diabetic states, the use of sulfonylurea is not advisable.

Interaction: The hypoglycemic actions of sulfonylurea may be potentiated by certain drugs including nonsteriodal anti-inflammatory drugs and other drugs that are highly protein bound salicylates, sulphonamides and chlormphenicol. When such drugs are administered to a patient receiving glipizide, the patient should be observed for hypoglycemia.

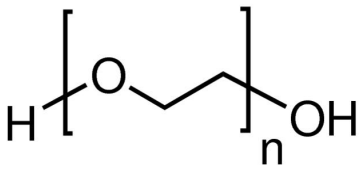
Side Effects: Hypoglycemia, gastrointestinal disturbances (nausea and diarrhea, one in seventy; constipation and gastralgia, one in one hundred), allergic reactions (erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in seventy patients), dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with glipizide.

Precaution: Patients should be instructed to closely follow their physician's prescription with regard to diet, dosage and schedule for taking the drug and should be taught to recognize promptly the early symptoms of hypoglycemia, that generally are headache, irritability, sleep disorders, tremor and heavy sweating, so they can contact a doctor in good time.

6.2 Excipient Profile[45]:

6.2.1 Poly Ethylene Oxide:

Table -4: Poly Ethylene Oxide Profile

Non-proprietary Names:	USP-NF: Polyethylene Oxide
Synonyms :	Polyox; polyoxiante; polyoxirane; polyoxyethylene.
Chemical Name and CAS Registry Number:	Polyethylene oxide [25322-68-3]
Empirical Formula:	$(CH_2CH_2O)_n$, where n represents the average number of oxyethylene groups.
Molecular Weight:	1 lakh to 70 Lakhs depends on their grade.
Structural Formula:	
Description:	White to off-white, free-flowing powder. Slight ammoniacal odor.
Functional Category:	Mucoadhesive; coating agent; tablet binder; thickening agent.
Applications:	Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water based formulations to provide improved viscosity stability. Polyethylene oxide films demonstrate good lubricity when wet.
Typical Properties:	
Angle of repose:	34º
Density (true):	1.3g/cm^3
Melting point:	65–70º C
Moisture content:	<1%

Solubility:	Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.
Stability and Storage Conditions:	Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.
Incompatibilities	Polyethylene oxide is incompatible with strong oxidizing agents.
Related Substances:	Polyethylene glycol.

6.2.2 Sodium Chloride:

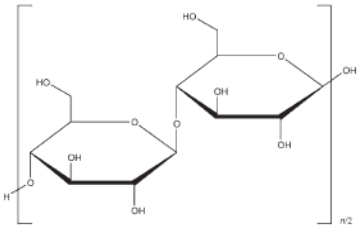
Table-5: Sodium Chloride Profile

Non-proprietary Names:	BP: Sodium Chloride JP: Sodium Chloride PhEur: Sodium Chloride USP: Sodium Chloride
Synonyms:	Alberger; chlorure de sodium; common salt; hopper salt; natural halite; rock salt; saline; salt; sea salt; table salt.
Chemical Name and CAS Registry Number:	Sodium chloride [7647-14-5]
Empirical Formula:	NaCl
Molecular Weight:	58.44
Structural Formula:	Cl-----Na^+
Description:	Sodium chloride occurs as a white crystalline powder or colorless crystals; it has a saline taste.
Functional Category:	Tablet and capsule diluent; tonicity agent;
Applications:	Sodium chloride has also been used as a channeling agent and as an osmotic agent in the cores of controlled-release tablets.
Typical Properties:	
Acidity/alkalinity:	pH = 6.7–7.3 (saturated aqueous solution)
Angle of repose:	38º for cubic crystals
Boiling point	1413ºC
Melting point:	804ºC
Density:	2.17 g/cm^3; 1.20 g/cm^3 for saturated aqueous solution.
Solubility:	In Water 1 in 2.8 at 20 ºC and 1 in 2.6 at 100ºC
Stability and Storage Conditions:	Aqueous sodium chloride solutions are stable but may cause the separation of glass particles from certain types of glass containers. Aqueous solutions may be sterilized by autoclaving or filtration. The solid material is stable and should be stored in

	a well-closed container, in a cool, dry place. It has been shown that the compaction characteristics and the mechanical properties of tablets are influenced by the relative humidity of the storage conditions under which sodium chloride was kept.
Incompatibilities:	Aqueous sodium chloride solutions are corrosive to iron. They also react to form precipitates with silver, lead, and mercury salts. Strong oxidizing agents liberate chlorine from acidified solutions of sodium chloride.
Related Substances:	Potassium chloride.

6.2.3 Cellulose, Microcrystalline:

Table-6: Cellulose, Microcrystalline Profile

Non-proprietary Names:	BP: Microcrystalline Cellulose JP: Microcrystalline Cellulose PhEur: Cellulose, Microcrystalline USP-NF: Microcrystalline Cellulose
Synonyms:	Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.
Chemical Name and CAS Registry Number:	Cellulose [9004-34-6]
Empirical Formula:	$(C_6H_{10}O_5)_n$ where n _ 220.
Molecular Weight:	36000
Structural Formula:	
Description:	Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.
Functional Category:	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
Applications:	Microcrystalline cellulose is widely used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline

	cellulose also has some lubricant and disintegrant properties that make it useful in tableting.
Typical Properties:	
Angle of repose:	Ceolus KG: 49º and Emcocel 90M: 34.4º
Density:	Bulk: 0.32 g/cm^3 for Avicel PH-101; Tapped: 0.45 g/cm^3 for Avicel PH-101;
Specific surface area:	1.06–1.12m^2/g for Avicel PH-101
Melting point:	Chars at 260-270 º C
Solubility:	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Stability and Storage Conditions:	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities:	Microcrystalline cellulose is incompatible with strong oxidizing agents.
Related Substances:	Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

6.2.4 Magnesium Stearate:

Table-7: Magnesium Stearate Profile

Non-proprietary Names:	BP: Magnesium Stearate JP: Magnesium Stearate PhEur: Magnesium Stearate USP-NF: Magnesium Stearate
Synonyms:	Dibasic magnesium stearate; magnesium distearate; magnesii stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.
Chemical Name and CAS Registry Number:	Octadecanoic acid magnesium salt [557-04-0]
Empirical Formula:	$C_{36}H_{70}MgO_4$
Molecular Weight:	591.24
Structural Formula:	$[CH_3(CH_2)_{16}COO]_2Mg$
Description:	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Functional Category:	Tablet and capsule lubricant.
Applications:	Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.
Typical Properties:	
Flowability:	Poorly flowing, cohesive powder.
Density:	Bulk: 0.159 g/cm^3; Tapped: 0.286 g/cm^3
Specific surface area:	1.6–14.8m^2/g
Melting point:	117-150ºC
Solubility:	Practically insoluble in ethanol, ethanol (95%), ether and water;

	slightly soluble in warm benzene and warm ethanol (95%).
Stability and Storage Conditions:	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities:	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Related Substances:	Calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate.

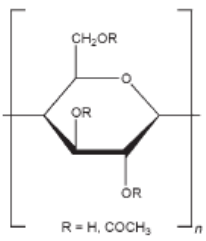
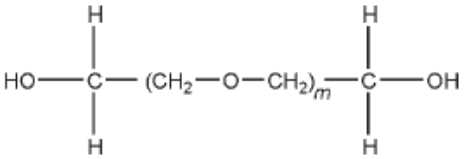
6.2.5 Iron Oxide (Yellow):

Table-8: Iron Oxide (yellow) Profile

Non-proprietary Names:	None adopted.
Synonyms:	E172; hydrated ferric oxide; iron (III) oxide monohydrate, yellow; pigment yellow 42; yellow ferric oxide.
Chemical Name and CAS Registry Number:	Iron oxide yellow [51274-00-1] (monohydrate); [20344-49-4] (hydrate)
Empirical Formula:	$Fe_2O_3\_H_2O$ (monohydrate); $FeHO_2$ (hydrate)
Molecular Weight:	Monohydrate - 177.70; hydrate - 88.85
Structural Formula:	Iron oxides are defined as inorganic compounds consisting of any one of or combinations of synthetically prepared iron oxides, including the hydrated forms.
Description:	Iron oxides occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and crystal structure.
Functional Category:	Colorant.
Applications:	Colorant.
Typical Properties:	
Density:	4.1 g/cm^3
Melting point:	1565ºC
Solubility:	Soluble in mineral acids; insoluble in water
Stability and Storage Conditions:	Iron oxides should be stored in well-closed containers in a cool, dry place.
Incompatibilities:	Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%.
Related Substances:	-

6.2.6 Opadry® CA:

Table-9: Opadry CA Profile

Opadry® CA, a ready formulated SPM coating system comprising Cellulose Acetate and Poly Ethylene Glycol 3350[46]		
	Cellulose Acetate	**Poly Ethylene Glycol**
Non-proprietary Names:	BP: Cellulose Acetate PhEur: Cellulose Acetate USP-NF: Cellulose Acetate	BP: Macrogols JP: Macrogol 400, Macrogol 1500 Macrogol 4000, Macrogol 6000 Macrogol 20000 PhEur: Macrogols USP-NF: Polyethylene Glycol
Synonyms:	Acetic acid, cellulose ester; acetyl cellulose; cellulose diacetate; cellulose triacetate; cellulosi acetas.	Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.
Chemical Name and CAS Registry Number:	Cellulose acetate [9004-35-7]	Poly ethylene glycol [25322-68-3]
Empirical Formula:	$[C_6H_7O_2(OH)_{3-m}(OOCCH_3)_m]$, m = 0~3	$HOCH_2(CH_2OCH_2)_mCH_2OH$ where m represents the average number of oxyethylene groups.
Molecular Weight:	38000 - 60000	PEG 3350: 3000 - 3700
Structural Formula:		
Description:	Cellulose acetate occurs as a hygroscopic white to off-	Polyethylene glycol grades 200–600 are liquids; grades 1000 and above

	white, free flowing powder, pellet, or flake. It is tasteless and odorless, or may have a slight odor of acetic acid.	are solids at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are free flowing milled powders.
Functional Category:	Coating agent; extended-release agent; tablet and capsule diluent.	Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.
Applications:	Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump-type tablets and implants.	Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.
Typical Properties:		
Density:	0.4 g/cm^3 for powders.	1.15–1.21 g/cm$_3$ at 25ºC
Melting point:	200-300ºC	48–54ºC for PEG 3000
Solubility:	The solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and dioxane.	Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil

Stability and Storage Conditions:	Cellulose acetate is stable if stored in a well-closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid	Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.
Incompatibili-ties:	Cellulose acetate is incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with the following plasticizers: diethyl phthalate, polyethylene glycol, triacetin, and triethyl citrate.	Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.
Related Substances:	Cellulose acetate phthalate.	Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

7. MATERIALS AND METHODS

7.1 Materials And Equipments:

7.1.1 List of Materials:

Table-10: List of materials used

S. No.	Materials Used	Manufacturer	Functional Category
1.	Anti-Diabetic Drug	Sri Krishna Drugs Limited, Hyderabad, India	Active Pharmaceutical Ingredient
2.	Poly ethylene oxide (6 lakhs MW)	Colorcon®, Goa, India	Controlled release polymer
3.	Poly ethylene oxide (3 lakhs MW)	Colorcon®, Goa, India	Controlled release polymer
4.	Poly ethylene oxide (50 lakhs MW)	Colorcon®, Goa, India	Controlled release polymer
5.	Poly ethylene oxide (70 lakhs MW)	Colorcon®, Goa, India	Controlled release polymer
6.	Sodium Chloride	Merck KGaA, Darmstadt, Germany	Channelizing Agent & Osmotic agent
7.	Iron oxide -yellow	Firmenich Inc., New Jersy, USA	Colorant
8.	Opadry CA	Colorcon®, Goa, India	Semi-permeable coat
9.	Opadry pink	Colorcon®, Goa, India	Top coat
10.	Magnesium Stearate USP NF	Covdien Mallinckrodt, Missouri, USA	Lubricant
11.	Microcrystalline cellulose (Avicel PH-101)	FMC Corporation health and Nutrition, Newark, USA	Diluents
12.	Ethanol	Hayman Ltd, Essex, UK	Solvent
13.	Acetone	Vertullus Performance, Grensboro, USA	Solvent
14.	Water	Purified water	Solvent

7.1.2 List of Equipments:

Table-11: List of Equipments used

S. No.	Equipments Used	Manufacturer
1.	Electronic Weighing balance	Mettler Toledo, India
2.	Sieve shaker	Retsch, Germany
3.	Rapid mixer granulator	Sams, India
4.	Rapid Dryer	Retch, USA
5.	Moisture Analyser	Sartorius, Germany
6.	Mechanical Sifter	Gansons, India
7.	Multi Mill	Gansons, India
8.	Octagonal Blender	Sams Techno Mech, India
9.	USP Tap density tester	Electrolab, India
10.	Compression machine (16 stations)	Cadmach, India
11.	Digimatic vernier caliper	Mitotoyo, Japan
12.	Friability Test Apparatus	Electrolab, India
13.	Varian Hardness tester	Varian Inc, USA
14.	Mechanical stirrer	Remi stirrers, India
15.	Coating Machine	Sams, India
16.	Dissolution apparatus	Electrolab, India
17.	UV Spectrophotometer	Perkin Elmer, USA
18.	Differential Scanning Calorimeter	Universal V4.5A, TA instruments, Delaware, USA
19.	X-Ray Diffractometer	D8 Advanced, Bruker Axs, Germany

7.2 Pre-Formulation Studies:

The following attributes were considered for API before initiating the formulation development:

- **Chemical characteristics**: Solubility and Stability
- **Physical Characteristics**: Particle size, flow characteristics, bulk density
- **Formulation Characteristics**: Assay, Friability, hardness, tablet weight, thickness, and effect of formulation variables on the dissolution profile.

A detailed understanding of the properties of drug substances is essential for minimizing formulation problems in later stage of drug development which will ultimately help in reducing the drug development cost and in decreasing time to reach the market.

The goal of the pre-formulation studies is to choose the correct form of the drug substance, to evaluate the physicochemical properties of drug and to generate a thorough understanding of the stability of the active pharmaceutical ingredient under the condition that will lead to development of an optimal drug delivery system.

7.2.1 Organoleptic Properties:

A small quantity of the drug powder was taken in butter paper and viewed in well-illuminated place for its colour, odour and taste.

7.2.2 Solubility:

Saturation solubility of drug using different dissolution media was performed initially as well as after 24 hours.

7.2.3 Melting Point:

Determination of melting point of the API sample was done using Differential Scanning Calorimeter using about 2 mg of API and empty pan as blank.

7.2.4 X-Ray Diffraction Studies:

X-Ray diffraction studies were performed on the drug sample to know whether it is crystalline or amorphous by using X-Ray Diffractometer.

7.2.5 Hygroscopicity Studies:

It is based upon the determination of equilibrium moisture content of samples equilibrated at particular relative humidity (RH) using saturated salt solutions in the well of the desiccators.

2g of the drug powder was taken in each of 4 previously tarred Petri dishes and incubated in desiccators equilibrated at 25°C and 80% RH using saturated salt solution of ammonium chloride. The samples were withdrawn at different time points of 2, 4, 8 and 24 h and checked for % weight gain and loss on drying (LOD). The initial LOD of the sample was also noted.

Table-12: Hygroscopicity classification criterion by sorption analysis.

Hygroscopic class	Criteria %w/w
Non-hygroscopic	< 0.2
Slightly hygroscopic	0.2–2
Hygroscopic/Moderately hygroscopic	2–15
Very hygroscopic	>15

7.2.6 Sieve Analysis:

Average size of the API's was determined using vibratory sieve shaker. 50g of API was weighed and placed on an sieve shaker. The test was carried out at amplitude of 50 for 15 minutes. Percentage retained on each sieve #20, #30, #40, #60, #80, #100 and fines were determined.

7.2.7 Moisture Content of API:

Moisture content of API was determined using Sartorius moisture analyzer with 1 g of powder sample at 105°C for 5 min. From the readings obtained, the percentage loss on drying was calculated.

7.2.8 Density:

7.2.8.1 Bulk Density:

An empty dry graduated 100 ml measuring cylinder was weighed accurately. 20 g of drug, which was previously passed through # 20 sieves, was transferred in the cylinder using a funnel. Powder was carefully leveled without compacting, and read the unsettled apparent volume (V_0). The filled cylinder was again weighed and the difference between initial and final weight was calculated to get the exact weight of powder (M) in the cylinder. Apparent bulk density in g/ml was calculated by the following formula:

Bulk density (BD) = Weight of powder (M) / Bulk volume (V_0)

7.2.8.2 Tapped Density:

Then the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using USP I method on tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute.

Cylinder was tapped for 500 times initially and then measured the tapped volume (V_1) was measured to the nearest graduated units, tapping was repeated for an additional 750 times and tapped volume (V_2) was measured to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2) should be taken.

The tapped density was calculated in g/ml by the following formula:

Tapped Density (TD) = Weight of powder (M) / Tapped volume (V_2)

7.2.8.3 Compressibility Index:

The compressibility index of the powder blend was determined by Carr's method. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD

7.2.8.4 Hausner's Ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's Ratio = TD / BD

Table-13: Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index (%)	Flow Character	Hausner's Ratio
< 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

7.2.8.5 Angle of Repose:

Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. The angle of repose is the constant three dimensional angle of a cone-like pile of material formed on a horizontal base.

$$\textit{Angle of repose } (\theta) = \tan^{-1} h/r$$

Table-14: Flow property and corresponding angle of repose as per USP

Flow Property	Angle of Repose (degrees)
Excellent	25 – 30
Good	31 – 35
Fair: aid not needed	36 – 40
Passable: may hang up	41 – 45
Poor: must agitate or Vibrate	46 – 55
Very Poor	56 – 65
Very, Very Poor	> 66

7.2.9 Drug- Excipient Compatibility Study:

Drug - Excipients compatibility study was carried out by placing drug alone or drug along with excipients in certain ratio in stoppered vials at 40˚C/75% RH and 50˚C for one month. Analysis of related substances of the mixture was carried out at initial and after 1 month.

Table-15: Drug-Excipient compatibility study

S. No.	Drug : Excipient	Ratio
1.	Glipizide	1
2.	Glipizide + Polyethylene oxide (3 lakhs MW)	1:10
3.	Glipizide + Polyethylene oxide (6 lakhs MW)	1:10
4.	Glipizide + Polyethylene oxide (50 lakhs MW)	1:10
5.	Glipizide + Polyethylene oxide (70 lakhs MW)	1:10
6.	Glipizide + Micro Crystaline Cellulose	1:5
7.	Glipizide + Sodium Chloride	1:5
8.	Glipizide + Opadry CA	1:10
9.	Glipizide + Iron oxide yellow	1:5
10.	Glipizide + Opadry pink	1:10
11.	Glipizide + Magnesium stearate	1:2

7.3 Characterization of Innovator Product:

The innovator product was tested for the following parameters.

7.3.1 Physical Properties of Innovator:

a) **Description:** The tablets were observed for their shape, color etc.
b) **Average weight (mg):** 20 tablets were weighed and their average weight was calculated.
c) **Thickness (mm):** Thickness of 10 tablets was measured using Vernier calipers.
d) **Dimension (mm):** The diameters of 10 tablets were measured using Vernier calipers.
e) **Hardness (Newton):** Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks. The hardness of tablet was measured by Varian hardness tester and results were expressed in kg/cm^2 or kp.
f) **Other parameters** like appearance, dosage form, batch no./lot no., expiry date, label claim, composition and storage recommendation were noted.

7.3.2 Dissolution Profile:

The *in-vitro* dissolution studies were performed using OGD media**.** The formulation development work has been focused on matching the dissolution profile with the innovator in the OGD media. The dissolution media and method details are given in Table-16.

Preparation of OGD Media:

For the preparation of 68.04 g of potassium dehydrogenate phosphate and 9.25g of sodium hydroxide was weighed and dissolved well in 10 liters water. The pH was adjusted to 7.5 by 2M Sodium hydroxide.

Table-16: Dissolution method referred from OGD[47]

Dissolution Medium	Simulated intestinal fluid without Pancreatin, pH 7.5
Apparatus	USP – II
RPM	50
Media volume	900 ml
Time interval	1,2,4,8,16 hours
Temperature	$37^0C \pm 2^0C$
Condition	Initial

7.4 Analytical Method Parameters

7.4.1 Standard Curve of Drug in Phosphate Buffer (pH 7.5):

It is one of the existing official drugs in USP. So, Based on these available information the drug detected at 276 nm λ_{max} using UV spectrophotometer. Accurately 100 mg of drug was dissolved in pH 7.5 phosphate buffer solution [PBS] in a 100 ml volumetric flask and the volume was made up to volume. From this stock solution, solutions containing 5, 10, 15, 25, 30 and 35 mcg/ml were prepared. The absorbencies of the solutions were measured spectrophotometrically using UV-Visible spectrophotometer at 276 nm against phosphate buffer solution pH 7.5 as blank.

7.5 Formulation and Development of OCDDS:

Formulation development studies were conducted in a step-by-step manner observing product characteristics and performance parameters like dissolution profile.

7.5.1 Calculation for the Quantity of Drug to be taken:

The quantity of API was arrived by the below mentioned calculation.

The assay as on such dried basis %w/w =

$$= \frac{\textbf{Assay on anhydrous basis x (100-LOD)}}{\textbf{100}}$$

Actual API per tablet = ***Theoretical API weight per tablet × 100 / Assay*** as such basis

Weight of the API was compensated with an equivalent weight of diluents.

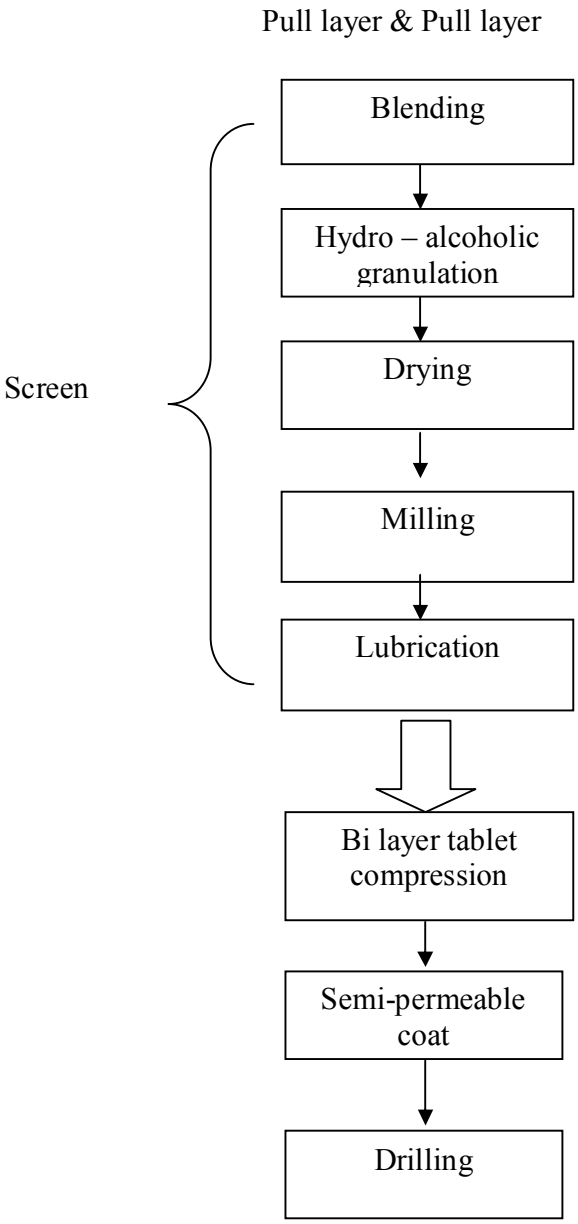
7.5.2 Selection of Excipient:

The selection of excipients was done considering the process selected i.e. push-pull technology[46,48]. The grade, and physical characteristics and properties of the excipients were selected accordingly. All the excipients used in the development trials were suitable for compression. The results of the excipient compatibility with the proposed excipients, justified the selection of the formulation composition.

7.6 Manufacturing Procedure:

Based on patent review and literature manufacturing of bi-layered push pull osmotic tablet was done as follows

Figure-26: Manufacturing procedure for push-pull osmotic tablet



7.7 Experimental Work:

7.7.1 Procedure

7.7.1.1 Drug / Pull Layer:

a) Dry Mixing:

API, microcrystalline cellulose, poly ethylene oxide and sodium chloride were first passed through 40# sieve to separate the agglomerates if any. The sifted powder was then dry mixed in rapid mixer granulator for 10 min.

b) Binder Solution:

Hydro-alcoholic solution was directly used as the binder liquid. Since polyethylene oxide has good binding properties no other agent was added. Solution up to 30% of the weight was used as the binder liquid.

c) Granulation:

Granulation is done by spraying the hydro-alcoholic solution for a period of 2 min and thereafter was knead for 2 min and 30 seconds.

d) Drying:

Wet mass was then transferred to Retsch drier and then dried for a period of 45 min using following as the set parameter.

Air flow - 40

Temperature - 40ºC

Time - 45 min

Drying was confirmed by subjecting it to LOD at a temperature of 70^0C in auto mode.

e) Sizing:

Dried granules were passed through 20# sieve.

f) Lubrication:

The above granules were lubricated with magnesium stearate for a period of 3 min in blender at 10 rpm.

7.7.1.2 Push Layer:

a) **Dry Mixing:**

Poly ethylene oxide, microcrystalline cellulose, sodium chloride and iron oxide were first passed through 40# sieve to separate the agglomerates if any. The sifted powder was then dry mixed in rapid mixer granulator for 10 min.

b) **Binder Solution**:

Ethanol was directly used as the binder liquid. Since polyethylene oxide has good binding properties, no other agent was added. Solution up to 30% of the weight was used as the binder liquid.

c) **Granulation:**

Granulation is done by spraying the ethanol solution for a period of 2 min and thereafter was kneaded for 2 min and 30 seconds.

d) **Drying:**

Wet mass was then transferred to Retsch drier and then dried for a period of 45 min using following as the set parameter.

Air flow - 40

Temperature - 40ºC

Time - 45min

Drying was confirmed by subjecting it to LOD at a temperature of 70°C in auto mode.

e) **Sizing:**

Dried granules were passed through 20# sieve.

f) **Lubrication:**

The above granules were lubricated with magnesium stearate for a period of 3 min in blender at 10 rpm

g) **Compression:**

The bi-layer tablet was compressed using the above prepared blend 1 and blend 2 using a bi-layer rotary compression machine. Lubricated granules were compressed using 9.5 mm standard concave punches, plain on both the sides in rotary compression machine

Table-17: Compression machine parameters

S. No.	Parameters	Description
1.	Machine	Cadmach
2.	Type of Tooling	''D''
3.	Punch shape	Shallow concave
4.	Punch dimensions (mm)	9.5 mm
5.	No. of punches	1
6.	Speed (rpm)	20
7	No. of Stations	16

7.7.1.3 Coating:

a) Preparation of Coating Solution:

- **Opadry CA:** Coating solution was prepared by dissolving Opadry CA in a mixture of acetone and water (9:1) and subjected under stirring for a period of 45 min.
- **Opadry Pink**: Colour coating solution was prepared by dissolving Opadry pink in water (1:10) and subjected under stirring for a period of 45 min.

b) Coating Process:

Coating was performed by prepared solution of Opadry CA using Sams India coater machine by setting the following process parameters:

Table-18: Coating machine parameters

Inlet temperature	30°C
Bed temperature	28°C
Pan rpm	8 to 12 rpm
Atomisation air pressure	2.0 psi

The average weight of the tablet was checked periodically to achieve required percentage weight gain. The coated tablet was allowed to dry at 40^0C in pan at 3 rpm.

c) Colour Coating:

Colour coating was performed by prepared solution of Opadry pink using Sams India coater machine by setting following process parameter.

Table-19: Coating machine parameters

Inlet temperature	50 °C
Bed temperature	45 °C
Pan rpm	8 to 12 rpm
Atomisation air pressure	2.0 psi

The average weight of the tablet was checked periodically to achieve required percentage weight gain. The coated tablet was allowed to dry at 40^0C in pan at 3 rpm.

d) Drilling of Orifice:

Orifice of diameter 0.5 mm was drilled on the push layer by using mechanical drill technology.

e) *In-Vitro* Dissolution Study:

The prepared tablet was then subjected to *in-vitro* analysis to select the best formulation by matching it with innovator.

7.8 Formulation Development:

Trials were performed in two stages:

7.8.1 Optimization of core tablet

- Optimization of PEO in push and pull layer.
- Optimization of osmogent in push layer.

7.8.2 Optimization of Semi-permeable membrane in push layer.

7.8.1 Optimization of Core Tablet

7.8.1.1 Optimization of PEO in Pull and Push layer:

From the literature and through understanding of reverse technology by checking the viscosity of the reference product it was found that polyethylene oxide of low and high molecular weight was used in pull and push layer respectively.

For optimization of pull layer, first low molecular weight polyethylene oxide (6 lakhs) was used with various concentrations initially from F1-F3 trials, since the results were unsatisfactory to increase the drug release, it was replaced by polyethylene oxide (3 lakhs) and trials F4-F6 were performed.

Similarly in push layer first high molecular weight polyethylene oxide (50 lakhs) is used with various concentrations initially from trials F1-F6, since the drug release was slow, it was replaced by Polyethylene oxide (70 lakhs) and trials F7-F9 were performed.

7.8.1.2 Optimization of Sodium Chloride in push layer:

Optimized trial F9 was taken, and to reduce the initial lag phase, trials F10 and F11 were performed by decreasing and increasing the concentration of sodium chloride in push layers respectively.

7.8.2 Optimization of Semi-Permeable Membrane:

Above optimized trial F11 was further selected for checking the effect of coating weight gain on drug release, trials F12, F13 and F14 were taken for 8%, 10% and 12% weight gain respectively.

7.9 Evaluation of Osmotic Tablets:

7.9.1 Assay:

Twenty tablets of formulation were crushed into a fine powder by mortar and pestle, 100 mg of the crushed powder was weighed in 100 ml volumetric and diluted in a flask with 7.5 phosphate buffer. After sonication for 15 min the diluted solution was filtered. The total amount of drug for each tablet was analyzed using UV spectrophotometer.

7.9.2 Weight Variation:

To study weight variation, 20 tablets of each formulation were weighed individually using a Sartorius electronic balance and compared with average value, the test was performed according to the official standards.

7.9.3 Hardness:

Ten tablets were randomly picked from each batch and checked for hardness using Varian hardness tester.

7.9.4 Thickness:

Ten tablets from each batch were randomly picked and checked for thickness using digimeter vernier calipers.

7.9.5 Friability:

Twenty tablets were weighed accurately and placed in the Electrolab friability apparatus. After 300 revolutions, the tablets were weighed and the percentage loss in tablet weight was determined.

7.9.6 *In-vitro* drug release studies:

In-vitro release rate was tested using (USP-II) paddle type dissolution apparatus, using 900 ml of pH 7.5 phosphate buffer as dissolution medium at temperature $37^{\circ} \pm 2^{\circ}C$. Samples were withdrawn at time intervals of 1, 2, 4, 8, and 16 hours and analyzed spectrophotometrically.

- For the final optimized formulation F14, the pre-compression parameter density and particle size distribution mentioned in pre-formulation studies were carried out.

7.10 Comparison of Dissolution Testing:

The tablets, which are prepared by the finalized formula is compared with the innovator by means of dissolution.

The method used for comparison of dissolution testing is model independent approach using difference factor f1.

Formula for Difference factor (f_1):

$$f_1=\{[\sum_{t=1}^{n}|R_t-T_t|] / [\sum_{t=1}^{n} R_t]\} * 100$$

Where, n = number of dissolution sample times

R_t and T_t is the individual or mean percent dissolved at each time point t, for the test and reference profiles respectively.

Formula for Similarity factor (f_2):

$$f_2 = 50 * \log \{[1+ (1/n) \sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5} * 100$$

A specific procedure to determine difference and similarity factors is as follows.

- The dissolution profile of two products (12 units each) of the test (prepared tablets) and reference (innovator tablets) were determined..
- Using the mean dissolution values from both curves at each interval, the difference factor (f1) and similarity factor (f2) using the above equations were calculated.
- For curves to be considered similar, f_1 values should be close to 0 and f_2 values should be close to 100. Generally, f1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves i.e. performance of test and reference products is similar.

7.11 Stability Studies:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and to establish a re-test period for the drug substance or a shelf-life for the drug product and recommended storage conditions.

The choice of test conditions defined in the guideline ICH – Q1A (R_2) is based on an analysis of the effects of climatic conditions in the three regions of the EU, Japan and the United States.

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies.

The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

7.11.1 Storage Conditions And Testing Frequency:

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Table-20: Stability study for trial batch

Study	Storage condition	Time period
Accelerated	40°C ± 2°C/75% RH ± 5% RH	3 months

8. RESULTS

8.1 Pre-Formulation studies:

8.1.1 Organoleptic Properties:

The following organoleptic characters are observed with API

Table-21: Organoleptic properties

Color	White to off white
Taste	Bitter
Odour	Characteristic

8.1.2 Solubility:

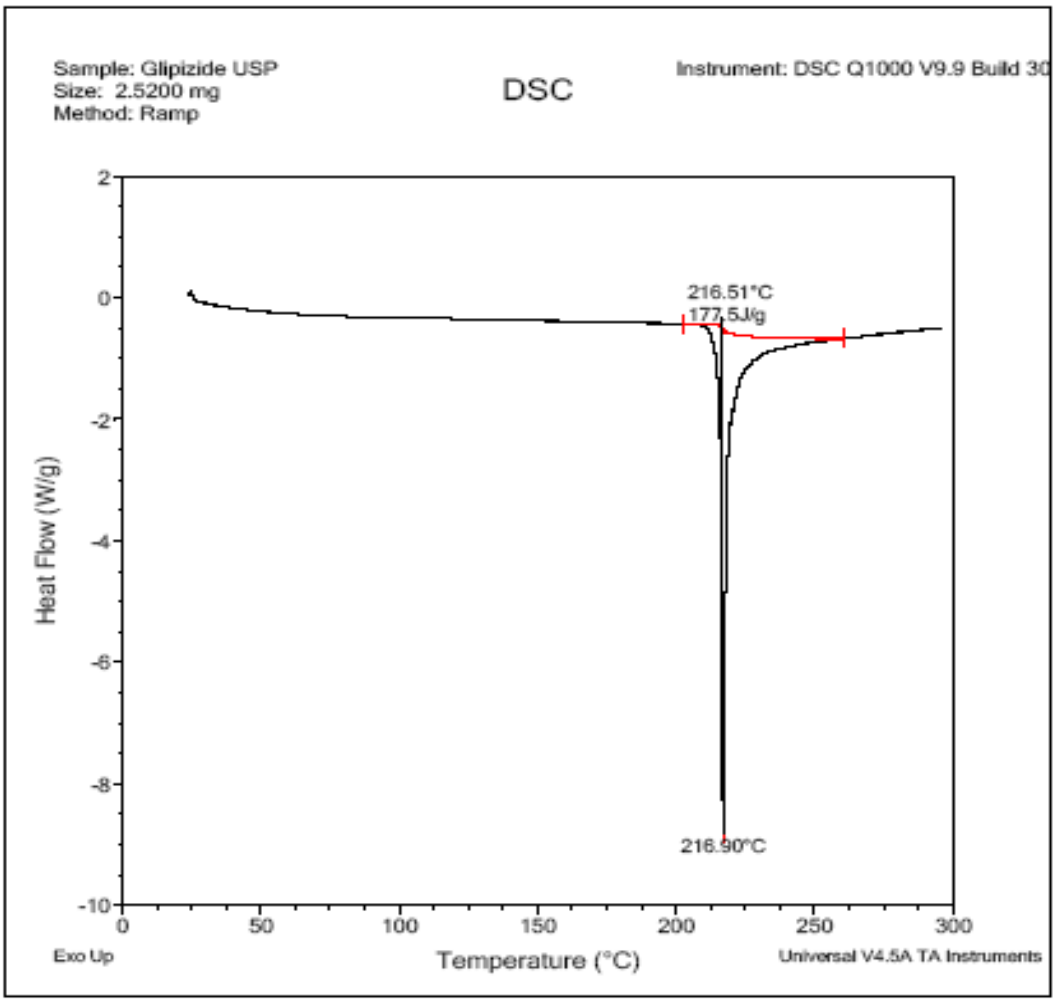
The saturation solubility of the drug candidate is tabulated below

Table-22: Solubility of the API in different media

Type of Media	**mg dissolved per 100 ml**			
	Initial		**24 hrs**	
	Individual	**Average**	**Individual**	**Average**
pH 5.5 Phosphate buffer	0.218 0.357	0.3	0.220 0.356	0.3
pH 6.8 Phosphate buffer	1.637 1.490	1.6	1.641 1.488	1.6
pH 7.5 Phosphate buffer	4.364 4.549	4.5	4.371 4.531	4.5

8.1.3 Melting Point:

The DSC thermogram of glipizide exhibited a broad endothermic peak at 216.51°C corresponding to its melting point of 216°C by using Universal V4.5A TA Instruments.



Peak Integration				
Start	Onset	Maximum	Stop	Area
°C	°C	°C	°C	J/g
203.05	216.51	216.9	260.28	177.5

Method Log:
1: Equilibrate at 25.00°C
2: Ramp 10.00°C/min to 300.00°C
3: End of method

Figure-27: DSC of Glipizide

8.1.4 X-ray Diffraction Study:

The X-ray diffraction pattern of powder sample was recorded on a scanning powder X-ray diffractometer.

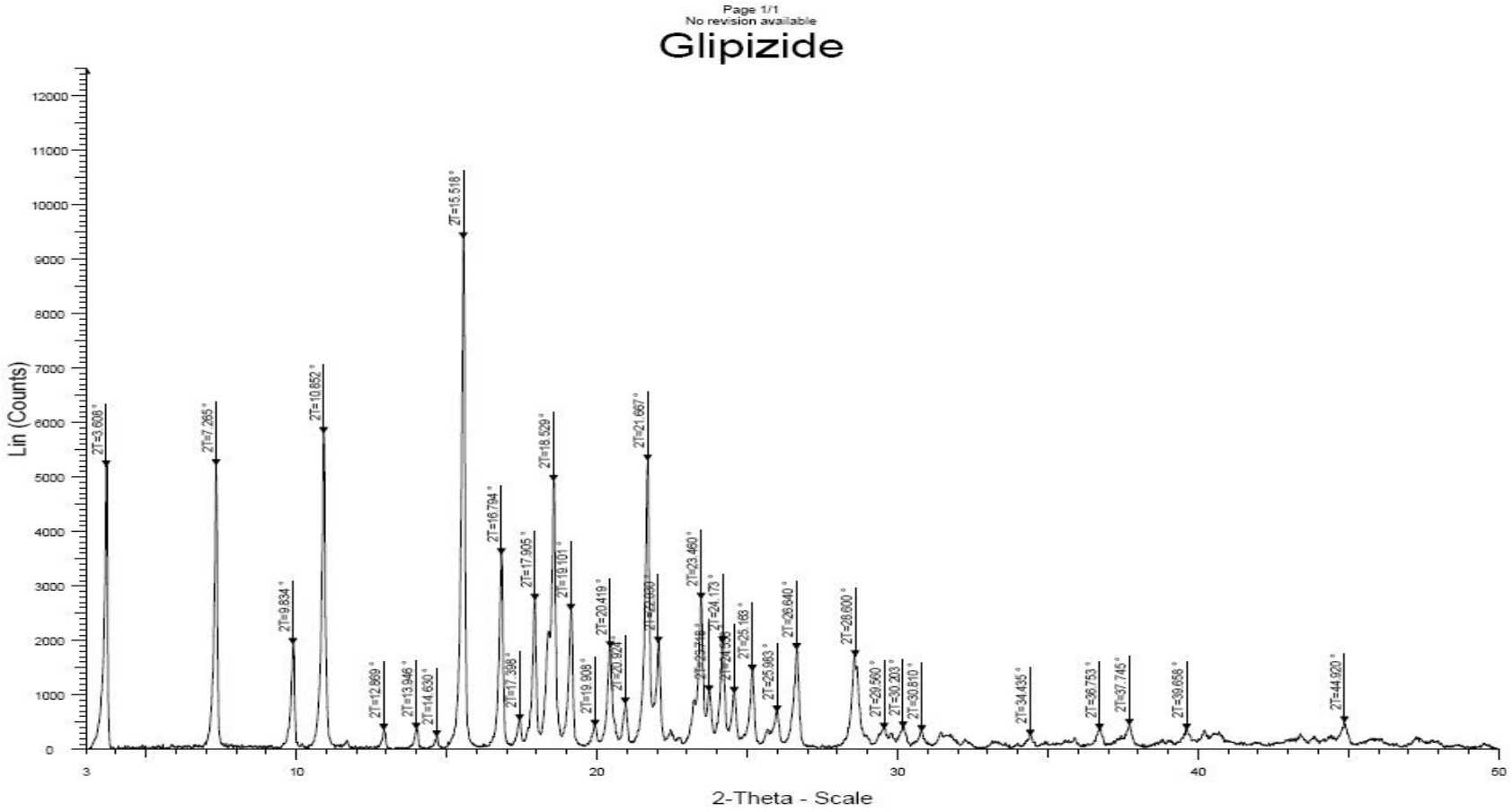


Figure-28: XRD graph of Glipizide

8.1.5 Hygroscopicity Studies:

As per the specifications of standards, hygroscopicity studies was carried out both in 25°C / 55% RH and 25°C / 80 % RH till 24 hours and the results are given in the following table.

Table-23: Observations of the hygroscopicity studies

Sr. No	Parameter	After 2nd hrs %	After 4th hrs %	After 8th hrs %	After 24th hrs %
I	Initial % LOD	0.59	0.59	0.59	0.59
II	RH 55% and 25°C				
1	% Weight gain	0.0	0.0	0.0	0.02
2	% LOD at 105°C for 5 min	0.60	0.59	0.62	0.62
III	RH 80 % and 25°C				
1	% Weight gain	0.0	0.0	0.01	0.025
2	% LOD at 105°C for 5 min	0.59	0.60	0.59	0.63

8.1.6 Sieve Analysis:

The data obtained from sieve analysis are tabulated below

Table-24: Particle size distribution of the API

Sieve no.	Retention % w/w
# 20	1
# 30	3.2
# 40	19.5
# 60	54.8
# 80	9.8
# 100	2.6
Through 100	8.6

8.1.7 Moisture Content of API:

Moisture content of the API by loss on drying was found to be 0.15% w/w.

8.1.8 Density:

Table-25: Physical characteristics of the API

S. No.	Parameter	Value
a)	Bulk density	0.17gm/ml
b)	Tapped density	0.28 gm/ml
c)	Carr's index	39.28
d)	Hausner ratio	1.65
e)	Angle of repose	44.13º

8.1.9 Drug-Excipient Compatibility Study:

The drug-excipients compatibility study carried out at 40˚C/75% RH for one month and the results are given below in table below. The physical appearance and assay of the mixture was carried out at initial and after 1 month.

Table-26: Drug-Excipient compatibility

S. No.	Drug-Excipient	Ratio	Condition	Physical Appearance	Assay (%)
1.	API	1	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	98.40
2.	API + PEO (6 lakh MW)	1:10	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	96.4
3.	API + PEO (3 lakhs MW)	1:10	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	98.6
4.	API + PEO (50 lakhs MW)	1:10	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	97.8

S. No.	Drug-Excipient	Ratio	Condition	Physical Appearance	Assay (%)
5.	API + PEO (70 lakhs MW)	1:10	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	98.4
6.	API +MCC	1:10	Initial	White crystalline powder	99.6
			40º/75% for 1 Month	No Change	96.8
7.	API + Sodium Chloride	1:5	Initial	White crystalline powder	99.6
			40º/75% for 1 Month	No Change	98.8
8.	API + Opadry CA	1:10	Initial	White to off white powder	99.6
			40º/75% for 1 Month	No Change	97.4
9.	API + Yellow Iron oxide	1:2	Initial	Yellow powder	99.6
			40º/75% for 1 Month	No Change	97.6
10.	API + Opadry pink	1:10	Initial	Pink powder	99.6
			40º/75% for 1 Month	No Change	98.4
11.	API + Magnesium stearate	1:1	Initial	White crystalline powder	99.6
			40º/75% for 1 Month	No Change	98.5

8.2 Characterization of Innovator Product:

8.2.1 Physical Properties of Innovator:

Table-27: Physical properties of innovator product

S. No.	Parameters	Innovator / Reference
1	Label Claim	Each Tablet contains 10 mg of Glipizide
2	Dosage form	Extended Release tablet
3	Batch No: / Lot No.	V130480
4	Expiry Date	May-17
5	Strength	10 mg/Tablet
6	Package insert	Available
7	Primary pack	HDPE container
8	Secondary pack	No
9	Composition	Polyethylene oxide, hypromellose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, Opadry® white
10	Storage	Store at 15-30^{0}C (59-86^{0}F)
11	Appearance [Embossing and break line details to be included]	White colored with no embossing imprinted GXL 10 on one side.
12	Average weight (mg)	392.25
13	Average thickness (mm)	5.55
14	Average diameter (mm)	9.82
15	Orifice diameter (mm)	0.43

Figure-29: Physical appearance of innovator tablet

Figure-30: Primary pack of innovator product

8.2.2 Dissolution Profile of Innovator:

Table-28: Dissolution profile of the marketed product

Time (h)	Percentage drug released
0	0
2	1
4	17
8	47
16	99
20	100
24	100

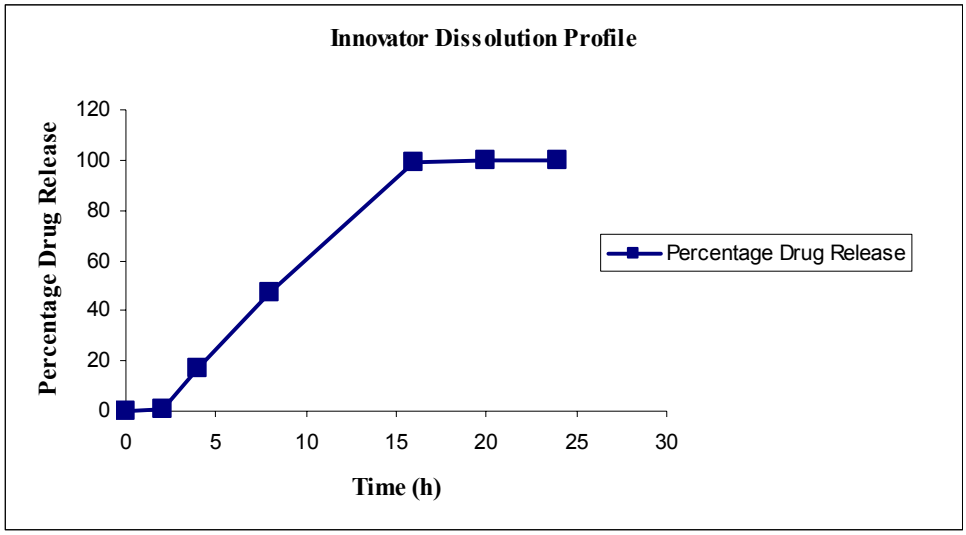


Figure-31: Innovators dissolution profile

8.3 Analytical Method Parameters:

Table-29: **Calibration curve of Glipizide in pH 7.5 phosphate buffer at λ_{max} 276 nm**

Concentration	Absorbance
0	0
5	0.145
10	0.255
15	0.362
20	0.469
25	0.625
30	0.772

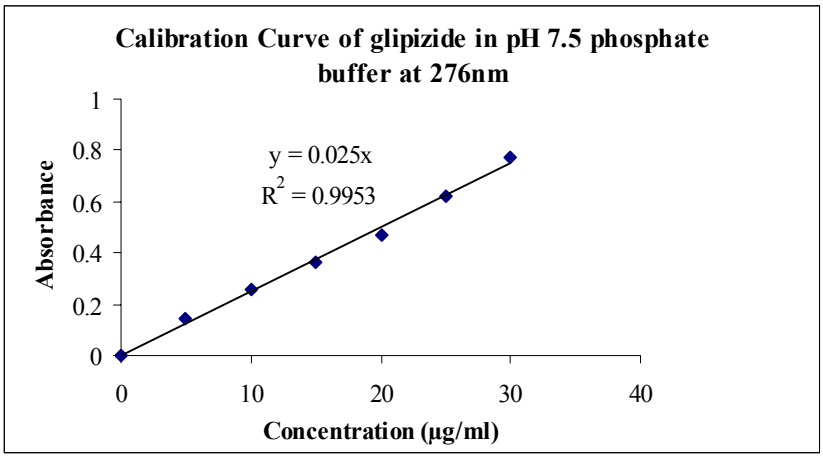


Figure-32: Calibration Curve of Glipizide

8.4 Formulation and Development of OCDDS:

8.4.1 Calculation for Quantity of Drug to be taken:

Assay on anhydrous basis (% w/w) = 99.60%

LOD/ water by Karl Fischer % w/w = 0.15%

The Assay as on such dried basis %w/w =

$$= \frac{\text{Assay on anhydrous basis} \times (100 - \text{LOD})}{100}$$

= 99.45%

Actual API per tablet = Theoretical API weight per tablet × 100/Assay as such basis

= 10.06 mg

Weight of the API was compensated with an equivalent weight of diluents.

8.4.2 Selection of Excipient:

The excipients were selected based on the available patent and literature support. Following excipients were considered.

- ✓ Poly Ethyelene Oxide (6 lakhs MW)
- ✓ Poly Ethyelene Oxide (3 lakhs MW)
- ✓ Poly Ethyelene Oxide (50 lakhs MW)
- ✓ Poly Ethyelene Oxide (70 lakhs MW)
- ✓ Sodium chloride
- ✓ Microcrystalline Cellulose
- ✓ Magnesium stearate
- ✓ Iron oxide yellow
- ✓ Opadry CA
- ✓ Opadry pink

8.5 Formulation Development:

8.5.1 Optimization of Core Tablet:

8.5.1.1 Optimization of Poly Ethylene Oxide in Push and Pull layer:

Table-30: Optimization of Polyethylene oxide in Pull and Push layers

Pull layer (drug layer)						
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Glipizide	10.06	10.06	10.06	10.06	10.06	10.06
Polyethylene oxide (6 lakhs MW)	145	160	175	---	---	---
Polyethylene oxide (3 lakhs MW)	---	---	---	145	160	175
Sodium chloride	10	10	10	10	10	10
MCC	45	30	15	45	30	15
Magnesium Stearate	1	1	1	1	1	1
Total	**211.06**	**211.06**	**211.06**	**211.06**	**211.06**	**211.06**
Push layer						
Polyethylene oxide (50 lakhs MW)	85	85	85	85	85	85
Sodium chloride	30	30	30	30	30	30
MCC	15	15	15	15	15	15
Iron oxide Yellow	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1
Total	**132**	**132**	**132**	**132**	**132**	**132**
Coating of Semi-Permeable membrane (14% gain)						
Opadry CA	48	48	48	48	48	48
Total	**391.06**	**391.06**	**391.06**	**391.06**	**391.06**	**391.06**
Colour coat (3% weight gain)						
Opadry pink	11.7	11.7	11.7	11.7	11.7	11.7
Total	**402.76**	**402.76**	**402.7**	**402.76**	**402.76**	**402.76**

8.5.1.2 Optimization of Poly Ethylene Oxide and Osmogent in Push Layer:

Table-31: Optimization of poly ethylene oxide and sodium chloride in Pull and Push layers

Pull layer (drug layer)					
Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**
Glipizide	10.06	10.06	10.06	10.06	10.06
Polyethylene oxide (3 lakhs MW)	175	175	175	175	175
Sodium chloride	10	10	10	10	10
MCC	15	15	15	15	15
Magnesium stearate	1	1	1	1	1
Total	**211.06**	**211.06**	**211.06**	**211.06**	**211.06**
Push layer					
Polyethylene oxide (70 lakhs MW)	80	85	90	90	90
Sodium chloride	30	30	30	20	40
MCC	20	15	10	20	0
Iron oxide Yellow	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1
Total	**132**	**132**	**132**	**132**	**132**
Coating of Semi-Permeable membrane (14% gain)					
Opadry CA	48	48	48	48	48
Total	**391.06**	**391.06**	**391.06**	**391.06**	**391.06**
Colour coat(3% weight gain)					
Opadry pink	11.7	11.7	11.7	11.7	11.7
Total	**402.76**	**402.76**	**402.76**	**402.76**	**402.76**

8.5.1.3 Optimization of Semi-Permeable Membrane in Push Layer.

Table-32: Optimization of semi-permeable membrane

Pull layer(drug layer)			
Ingredients (mg)	**F12**	**F13**	**F14**
Glipizide	10.06	10.06	10.06
Polyethylene oxide (3 lakhs MW)	175	175	175
Sodium chloride	10	10	10
MCC	15	15	15
Magnesium Stearate	1	1	1
Total	**211.06**	**211.06**	**211.06**
Push Layer			
Polyethylene oxide (70 lakhs MW)	90	90	90
Sodium chloride	40	40	40
MCC	0	0	0
Iron oxide Yellow	1	1	1
Magnesium Stearate	1	1	1
Total	**132**	**132**	**132**
Coating of Semi-Permeable membrane			
	8%	**10%**	**12%**
Opadry CA	27.4	34.3	41.1
Total	**370.46**	**377.36**	**384.16**
Colour coat (3% weight gain)			
Opadry pink	11.1	11.3	11.5
Total	**381.56**	**388.66**	**395.66**

Figure-33: Side view of uncoated bi layered, Semi-permeable membrane coated, Top coated osmotic tablets

Figure No 34: Top view of coated osmotic tablet with drilling

8.6 Evaluation of Osmotic Tablets:

8.6.1 Compression Parameters

Table-33: Compression parameters of trials F1-F14

Batch No.	Assay (%)	Average Weight (Bi-layer tablet) mg	Hardness (kp)	Thickness (mm)	Friability (%)	Weight variation
F1	98.06	341.3 ± 0.56	13 ± 0.26	4.95 ± 0.13	0.118	Complies
F2	102.3	343.8 ± 1.26	14 ± 0.36	4.92 ± 0.24	0.137	Complies
F3	99.1	344.8 ± 1.53	14.8 ± 0.4	4.93 ± 0.19	0.154	Complies
F4	103.2	343.4 ± 0.29	14 ± 0.28	4.93 ± 0.26	0.241	Complies
F5	101.0	341.6 ± 2.10	13 ± 0.40	4.94 ± 0.22	0.148	Complies
F6	98.7	342.6 ± 0.12	13.6 ± 0.25	4.93 ± 0.16	0.160	Complies
F7	102.07	342.8 ± 2.01	13.5 ± 0.33	4.90 ± 0.28	0.213	Complies
F8	98.6	344.8 ± 1.02	14.8 ± 0.38	4.91 ± 0.22	0.256	Complies
F9	99.8	341.2 ± 2.06	13 ± 0.22	4.92 ± 0.17	0.222	Complies
F10	96.7	345.4 ± 0.75	15 ± 0.28	4.91 ± 0.15	0.157	Complies
F11	100.8	341.5 ± 1.96	13 ± 0.40	4.90 ± 0.23	0.250	Complies
F12	98.6	342.2 ± 1.25	13.8 ± 0.62	4.93 ± 0.15	0.231	Complies
F13	101.2	343.6 ± 0.46	14 ± 0.23	4.95 ± 0.13	0.168	Complies
F14	99.05	341.3 ± 0.26	13 ± 0.26	4.96 ± 0.08	0.226	Complies

8.6.2 *In- Vitro* Dissolution of Push-Pull Osmotic Drug Delivery System:-

The results of dissolution profile for the various formulations trials for bi-layer osmotic drug delivery system are as follows

8.6.2.1 Optimizations of Poly Ethylene Oxide in Pull and Push Layer

Table-34: Percentage cumulative drug release data

Time (h)	Innovator	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	1	1	2	1	1	1	1
4	17	10	13	11	9	10	13
8	47	24	30	25	28	32	28
16	99	45	48	55	74	70	77
20	100	55	58	63	77	77	82
24	100	56	62	65	78	80	84

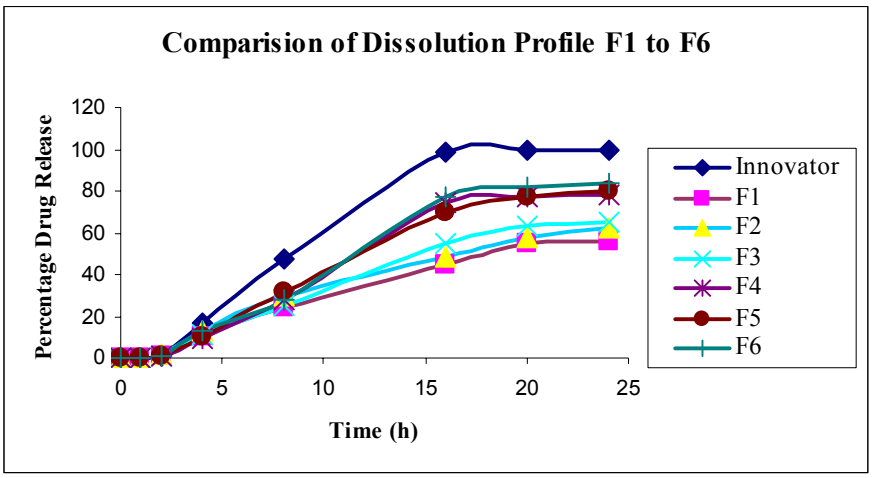


Figure-35: Percentage cumulative drug release against time graph

8.6.2.2 Optimizations of Poly Ethylene Oxide in Pull and Push Layer:-

Table-35: Percentage cumulative drug release data

Time (h)	Innovator	F7	F8	F9
0	0	0	0	0
1	0	0	0	0
2	1	1	1	1
4	17	7	9	10
8	47	28	26	33
16	99	68	77	93
20	100	82	91	96
24	100	84	92	96

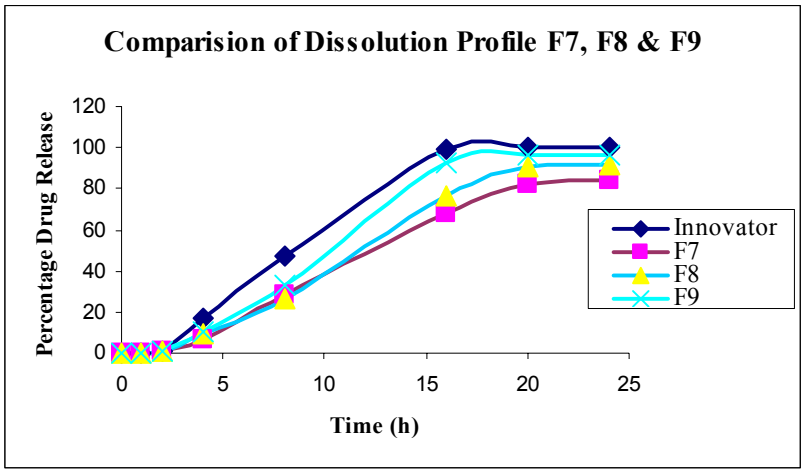


Figure-36: Percentage cumulative drug release against time graph

8.6.2.3 Optimization of Sodium chloride in Push Layer:-

Table-36: Percentage cumulative drug release data

Time (h)	Innovator	F10	F11
0	0	0	0
1	0	0	0
2	1	1	1
4	17	8	15
8	47	30	46
16	99	93	99
20	100	95	99
24	100	96	100

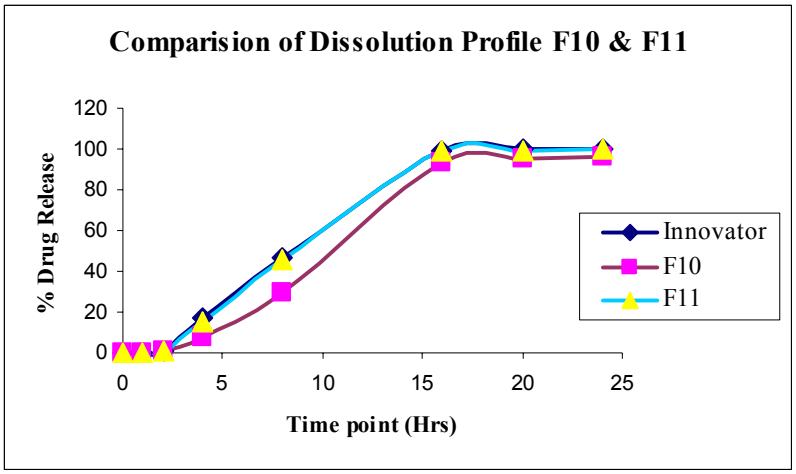


Figure-37: Percentage cumulative drug release against time graph

8.6.2.4 Optimization of Semi-Permeable Membrane Coating:-

Table-37: Percentage cumulative drug release data

Time (h)	Innovator	F12	F13	F14
0	0	0	0	0
1	0	6	2	0
2	1	9	4	1
4	17	30	22	17
8	47	62	56	49
16	99	100	100	99
20	100	100	100	100
24	100	100	100	100

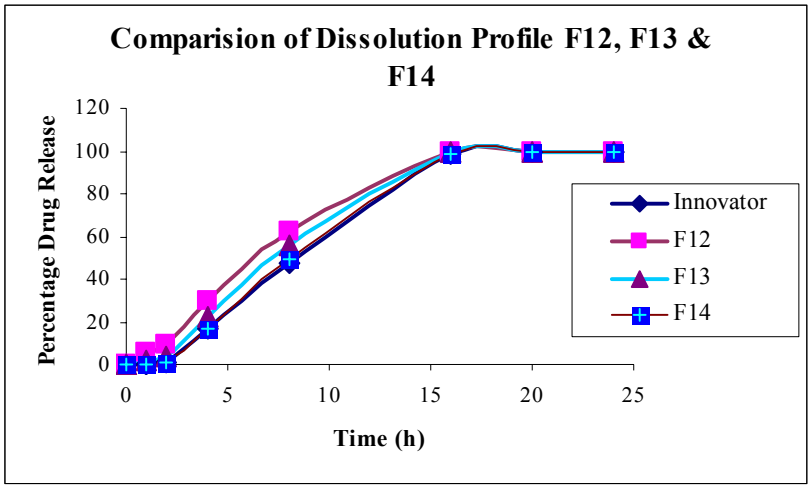


Figure-38: Percentage cumulative drug release against time graph

8.6.2.5 Comparison of Formulation F11 and Formulation F14:

Table-38: Percentage cumulative drug release data

Time (h)	Innovator	F11	F14
Coating of Semi-permeable membrane		14%	12%
0	0	0	0
1	0	0	0
2	1	1	1
4	17	15	17
8	47	46	49
16	99	99	99
20	100	99	100
24	100	100	100

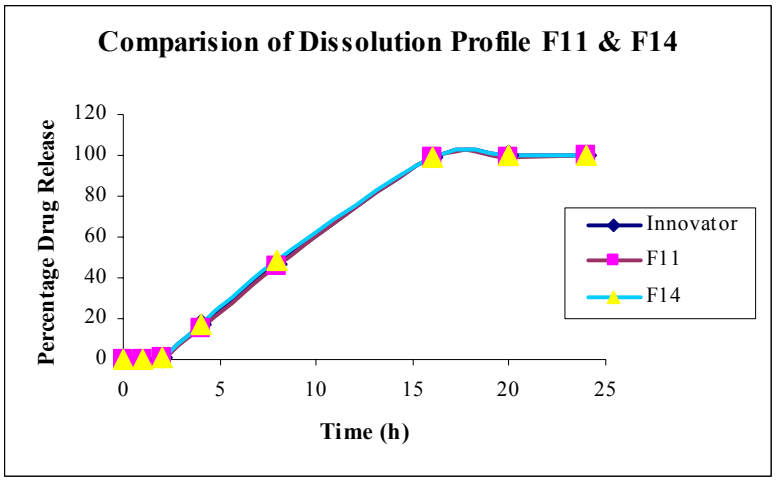


Figure-39: Percentage cumulative drug release against time graph

8.7 Dissolution Profile Comparison (Test formulation against Reference formulation):

8.7.1 Test formulation F14 against Reference formulation:

Table-39: Comparison of Dissolution profile of test vs reference

Time (h)	Rt	Tt	|Rt-Tt|	$\|Rt-Tt\|^2$
0	0	0	0	0
2	1	1	0	0
4	17	17	0	0
8	47	49	2	4
16	99	99	0	0
20	100	100	0	0
24	100	100	0	0
Total	364	366	2	4

$$f_1 = \{[\sum_{t=1}^{n}|R_t-T_t|] / [\sum_{t=1}^{n} R_t]\} * 100$$

$$= 1$$

$$f_2 = 50 * \log \{[1+ (1/n) \sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5} * 100$$

$$= 92$$

8.7.2 Test formulation F11 against Reference formulation:

Table-40: Comparison of Dissolution profile test vs standard

Time (h)	Rt	Tt	|Rt-Tt|	$\|Rt-Tt\|^2$
0	0	0	0	0
2	1	1	0	0
4	17	15	0	0
8	47	46	2	4
16	99	99	0	0
20	100	99	0	0
24	100	100	0	0
Total	364	360	2	4

$$f_1 = \{[\sum_{t=1}^{n}|R_t-T_t|] / [\sum_{t=1}^{n} R_t]\} * 100$$

$$= 1.10$$

$$f_2 = 50 * \log \{[1+ (1/n) \sum_{t=1}n (R_t-T_t)^2]^{-0.5} * 100$$

$$= 93$$

8.8 Physical Characteristics of Optimized Formulation.

8.8.1 Physical Characteristics of Lubricated Blend F14:

The physical characteristic and particle size analysis of lubricated blend was studied and listed below.

Table-41: Physical characteristics of lubricated blend F14

Parameters	Pull layer	Push layer
Bulk density (g/ml)	0.45	0.511
Tapped density (g/ml)	0.52	0.58
Carr's index (%)	14.2	12.3
Hausner's ratio	1.15	1.14
Angle of repose	26.57	24.7

Table-42: Particle size analysis results

Sieve Number	Percentage weight retained on sieve	
	Pull layer	Push layer
20	0	0.4
30	5.6	2
40	7.9	3.2
60	20.2	33.6
80	21.4	21
100	10.9	8.2
Pan	33.8	31.6

8.8.2 Physical Characteristics of Coated Tablets of F14 Batch:

The physical characteristics of the coated tablets of formulation F14 was studied and listed below.

Table No. 43: Physical characteristics of the coated tablets of F14 batch

S. No.	Parameters	F14
1	Average weight	396.8+1.96
2	Friability (%)	0.19
3	Hardness (kp)	25 ± 2.1
4	Thickness (mm)	5.66 ± 0.06
5	Average diameter	9.0 ± 0.8

Figure-40: Optimized batch (F14) Osmotic tablets

8.9 Stability Data of Optimized Formulation:

The samples of F14 batch were kept under 40ºC/75% RH condition for 1 month. The Physical appearance, assay and dissolution profile of initial and 1 month data were studied and listed below.

Table-44: Stability data of F14 batch

S. No	Test		Initial	40ºC/75% RH 1 month	40ºC/75% RH 3 month
1.	Physical Appearance		Pink coloured smooth faced tablet	No Change	No Change
2.	Assay (%)		99.05	99.56	100.20
3.	Dissolution release profile (%)	2 hrs	1 ± 0.58	1 ± 0.58	2 ± 0.58
		8 hrs	49 ± 5.69	50 ± 4.04	48 ± 6.51
		16 hrs	99 ± 1.15	97 ± 3.06	98 ± 2.08

9. DISCUSSION

9.1 Pre-Formulation Studies:

9.1.1 Organoleptic Properties:

The organoleptic properties of active pharmaceutical ingredient of this study (Glipizide) was studied and found to be White to off white in colour, bitter in taste and odourless.

9.1.2 Solubility:

The saturation solubility of the drug candidate is tabulated in Table 22. The solubility study of glipizide was carried out and it was observed that it has pH dependent solubility, soluble in pH 7.5. Also literature survey reveals that glipizide is a highly permeable drug. Hence it was concluded that model drug belongs to BCS class II i.e. it has low solubility and high permeability.

9.1.3 Melting Point:

The DSC thermogram (Figure 27) of glipizide exhibited a broad endothermic peak at 216.51°C corresponding to its melting point of 216°C by using Universal V4.5A TA Instruments. Therefore it was concluded that exposure to high temperature should be avoided and the loss on drying percentage of the blends prepared should be taken at temperature fairly below the melting point of the drug.

9.1.4 X-ray Diffraction Study:

X- ray powder diffraction patterns were recorded (Figure 28) using X-ray Diffractometer, D8 Advanced, Bruker AXS, Germany. The scanning rate used was 1^{o}. 2θ/min over the range 3 to 50. The X-ray diffraction pattern showed that glipizide is crystalline in nature.

9.1.5 Hygroscopicity Studies:

Hygroscopicity studies was carried out both in 25°C/55% RH and 25°C/80% RH till 24 hours.

As per standard, increase in weight gain was within limits and as percentage weight gain of glipizide was found to be 0.02% and 0.025% at RH 50% and 80% after 24 hours respectively (Table 23), Thus glipizide was found to be non-hygroscopic in nature.

9.1.6 Sieve Analysis:

From the sieve analysis result listed in Table 24, it was found that majority of the particles lie above sieve no #60 (250 μm).

9.1.7 Moisture Content of API:

Moisture content of the glipizide by Loss on Drying was found to be 0.15% w/w.

9.1.8 Density:

The values of Carr's index, Hausner ratio and angle of repose showed that the glipizide powder has very poor flow (Table 25).

9.1.9 Drug-Excipient Compatibility Study:

The excipients compatibility study results (Table 26) showed that the assays of the mixture were within specified limits and no physical changes were observed. Thus all the above excipients were said to be compatible with glipizide and can be used in formulation development.

9.2 Characterization of Innovator Product:

9.2.1 Physical Properties of Innovator:

Physical properties of innovator product were noted and listed in Table-27.

9.2.2 Dissolution Profile of Innovator

The dissolution of the innovator Tablet was done in USFDA recommended media (simulated intestinal fluid without pancreatin, pH 7.5) and the percentage drug released is tabulated in Table 28.

9.3 Analytical Method parameters:

9.3.1 Calibration Curve of Glipizide in pH 7.5 Phosphate Buffer

Placebo Interference:

The placebo solution does not show any peak at the λ_{max} of standard solution of the model drug. Therefore no placebo interference was encountered during the dissolution of prototype formulation.

Inference:

The λ_{max} of glipizide was observed at about 276 nm. Considering this λ_{max}, a calibration curve of glipizide was plotted (Figure 32). The standard graph constructed conferred that the concentrations of drug ranging from 5 to 30 µg/ml obeyed the Beer-Lambert's Law principle. Moreover, the calibration curve exhibited a good correlation between the concentrations and the absorbance in this range ($R^2 = 0.9953$).

9.4 Evaluation of Osmotic Tablets:

9.4.1 Compression Parameters:

It was evident from the Table 33 that all the trial formulations comply with the standard specification mentioned in the USP for assay, average weight, weight variation and friability. Also the thickness and hardness parameters of the prepared Tablets complied with the in house specifications. The orifice diameter was found to be in the range of 0.53 to 0.56 mm.

9.4.2 *In-Vitro* Dissolution of Push-Pull Osmotic Drug Delivery System:

Dissolution profile results for the various formulation trials of push and pull technique based osmotic drug delivery system are as follows:

9.4.2.1 Optimizations of PEO in Pull and Push Layer:

Among the formulations, F1 to F6 when compared with innovator (Table 34), the results of percentage cumulative release of formulation F5 and F6 showed good zero-order release kinetics (Figure 35). F6 showed a

higher percentage cumulative release compared to F5 and also F6 showed a release profile closer to the innovator.

9.4.2.2 Optimizations of PEO in Pull and Push Layer:

Based on dissolution profile of the trials of F7 to F9 (Table 35), it was found that as the concentration of PEO in the push layer is increased, cumulative percentage of the drug release is also increased. From the above trials it was found that formulation F9 showed good zero-order release kinetics. Since F9 showed a good percentage cumulative release close to innovator, it was selected for further optimization (Figure 36).

9.4.2.3 Optimization of Sodium Chloride in Push Layer:

After optimizing the Sodium chloride in push layer, the dissolution profile of formulation F10 and F11 clearly showed that when the concentration of sodium chloride in push layer is increased, the initial drug release was increased (Table 36 and Figure 37). Among, F10 and F11, formulation F11 showed release rate closer to innovator and had greater f_2 value. As the f_2 and the dissolution profile showed positive signs among other formulation, F11 formulation was taken as the final core formula.

9.4.2.4 Optimization of Semi-Permeable Membrane Coating:

To investigate the role of semi-permeable membrane in the formulation, three formulations with 8%, 10% and 12% were formulated and evaluated. From the results in Figure 38, it was seen that all the formulation showed good zero order release kinetics. Formulations F12 and F13 showed faster percentage drug release compared with formulation F14 (Table 37). However formulation F14 showed similar release profile when compared with innovator.

9.4.2.5 Comparison of Formulation F11 and Formulation F14:

When the release profile of formulation F11 and F14 were compared against the innovator, the release was found to be similar (Table 38). Increase in coating (i.e. more than 14%) in semi permeable membrane

may further decrease the release profile. Correspondingly, decrease in coating (i.e. 8 to 10%) showed faster profile compared with that of innovator (Formulation F12 and F13).

The Formulation F14 with 12% coating and F11 with 14% coating were closer to the release profile of reference formulation (Figure 39), therefore a coating of 13±1% will suffice to meet the study requirements.

9.5 Dissolution Profile Comparison (Test product v_s. Reference product):

As formulations F11 and F14 % had cumulative percentage drug release were closer to the innovator release profile, they both were selected for finding out the difference factor (f_1) and similarity factor (f_2).

The f_1 and f_2 values obtained from both formulations were within the limits. So the prepared F11 and F14 formulations were found to be equivalent with innovator. More specifically F14 shows the better closeness to the innovator product.

As both F11 and F14 are having the same composition in the core Tablet and they vary in coating of semi permeable membrane with 2% each, optimum range for the coating of semi-permeable membrane can be considered as 13±1%.

But, to avoid extra weight gain when compared to other formulations, 12% is selected as optimized weight gain, concluding F14 as optimized formulation and continuing further studies to scale-up formulations.

9.6 Physical Characteristics of Optimized Formulation:

9.6.1 Physical Characteristics of Lubricated Blend F14:

The physical characteristic of lubricated blend of F14 was studied and listed (Table 41). Both the push layer and pull layer blends were found to have good flow property.

9.6.2 Physical Characteristics of Coated Tablets of F14 Formulation:

The average weight, friability, hardness, thickness and average diameter of the coated Tablets of f14 formulation were studied and they were found to be acceptable (Table 43).

9.7 Stability Data of Optimized Formulation:

Optimized formulation was kept for stability studies and checked for the appearance, assay, and dissolution profile after 1 and 3 months (Table 44). There were no significant changes in i*n-vitro* release profile. Thus, formulation F14 was found to be stable with respect to our desired parameters.

10. SUMMARY AND CONCLUSION

The aim of the present study was to formulate and evaluate a generic osmotic controlled delivery system for an innovator's anti-diabetic drug. Osmotic devices are most promising strategy based systems for controlled drug delivery. They are among the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems or implantable devices. Extended release formulation of an anti-diabetic drug based on push pull osmotic technology was developed and evaluated. The effect of different formulation variable namely, amount of PEO in push and pull layers, effect of various grades of PEO in push and pull layers, amount of sodium chloride in push layer, semi permeable membrane weight gain, were studied.

Bi-layer push-pull osmotic tablets were prepared using polyethylene oxide as an expanding agent. Tablets were coated with semi permeable membrane using Opadry CA and mechanically drilled; *in vitro* drug release was performed in US food and drug administration recommended official dissolution media pH 7.4 phosphate buffer to study the drug release profile.

From formulations F1 to F3, poly ethylene oxide of molecular weight 6 lakhs and poly ethylene oxide of molecular weight 50 lakhs were used in pull and push layers respectively with varying concentrations, the drug release profile showed very slow release. To enhance the drug release, formulations F4 to F6 were formulated using poly ethylene oxide of 3 lakhs molecular weight, which is of low molecular weight when compared to previous formulation. When poly ethylene oxide of 50 lakhs was used in push layer, the release profile showed good zero-order release but the drug release was slow compared with that of innovator.

To enhance the drug release further, formulations F6 to F9 were done using PEO of higher molecular weight, 70 lakhs in push layer, and PEO of 3 lakhs molecular weight in pull layer. It showed good release profile similar to innovator, but initial drug release was slow.
Formulations F10 and F11 were performed to overcome the initial slow release of drug, by varying concentration of sodium chloride in push layer. By increasing the concentration of Sodium chloride the drug release was increased and the release profile was similar to innovator.

All the above formulations were performed by coating with Opadry CA (a ready formulated semi permeable membrane coating system comprising CA and PEG3350) as semi permeable membrane to get a 14% weight gain, based on information available from patent and literature. To check the effect of weight gain, formulations F12, F13, F14 were formulated by coating with Opadry CA to obtain, 8%, 10%, 12% weight gain respectively. Formulation F12 and F13 with 8% and 10% showed fast release, whereas, the formulation F14 with 12 % showed similar release when compared with innovator. The comparative release profile of formulations with 12% and 14% showed similar release profile when compared with innovator. So, coating of semi-permeable membrane of 13±1% can be recommended to get the desired release profile. But, to avoid extra weight gain when compared to other formulations, 12% was selected as optimized weight gain, concluding F14 as optimized formulation and continuing further studies to scale-up formulations.

Stability studies were conducted at 40ºC/75% RH for 3 months. Physical appearance, assay and dissolution profile of optimized formulation F14 complies with Innovator product and was found to be stable.

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